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TREATMENT OF BLEEDING FROM PORTAL HYPERTENSION IN PATIENTS WITH CIRRHOSIS OF THE LIVER*

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THE greatest problem today in the management of patients who bleed massively from the upper gastrointestinal tract is afforded by the group with chronic liver disease and portal hypertension. Most of these patients bleed from varices at the gastroesophageal junction. The mortality in these patients is extremely high, in contrast to that in patients who bleed from gastroduodenal ulcer. A program of surgical intervention has been worked out for the ulcer group, and, when surgery is used with good judgment, the outlook is reasonably good for patients bleeding from gastric or duodenal ulcers. The same statement does not apply in hemorrhage from esophageal varices. A great deal of progress has been made in the prevention of hemorrhage in patients with portal hypertension, mostly by the employment of portacaval shunts in patients who have been fortunate enough to survive one or more hemorrhages, but it is doubtful if the situation is much better in the management of the bleeding episode today than it was ten years ago, despite several innovations in treatment. Exceptions to this statement can be allowed for certain clinics. The ubiquitous use of tamponade of the gastroesophageal region must have had some good effect, and the active program of ligation of the bleeding varices offers promise. Everyone must admit, however, that this problem is complex and far from solved.

If it were only exsanguination and a bleeding lesion that presented itself, the situation would be quite like that in a bleeding ulcer except for the anatomic site involved. But it is the profound and rather unpredictable effect of the associated liver disease and liver dysfunction that makes the great difference. There are a few patients who have portal hypertension as the result of extrahepatic portal-vein obstruction of a developmental or acquired origin who bleed from esophageal varices. These patients have a normal liver and make up approximately 10 per cent of all patients with portal hypertension in most general hospitals. Although they may die of exsanguination, especially if not well attended, they do not present the same serious problems that patients with cirrhosis of the liver do. The life history of this group of rather young patients with extrahepatic portal venous block has not yet been written. Their outlook is not good for long life, even when portacaval shunts have been performed as a preventive measure, for reasons that cannot be taken up in this report. But since they do not present so many problems during hemorrhage as patients with liver disease they are not considered in this communication. Only patients with cirrhosis of the liver who have bled are discussed.

It is the purpose of this report to present the results of a study made on 50 consecutive patients admitted to the Albany Medical Center,** who bled massively and who had cirrhosis of the liver. In the discussion of this paper, a program that we believe will reduce the mortality rate of hemorrhage in these patients is presented. This program has been evolved from an appraisal of the results of this study in addition to the employment of measures suggested in the more recent literature on the subjects of liver disease and gastrointestinal bleeding.

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**Thirty-four patients were observed in the Albany Hospital during the years 1946 through 1953 and 16 patients were treated in the Veterans Administration Hospital between July 1, 1951, and December 31, 1953.

Clinical Material

The clinical records of 50 consecutive patients who had been admitted to the hospital and treated for massive upper gastrointestinal hemorrhage as a result of chronic liver disease and portal hypertension have been reviewed, and the data on this group are submitted to show the problem that exists. First of all, the diagnosis in these patients needs to be established since a reasonable argument of the validity of certain assumptions may exist if this question is not settled.

Hemorrhage

Each patient had to fulfill certain criteria to be included in this study. In the first place, all patients had a large hemorrhage and good evidence for the diagnosis of portal hypertension. A massive hemorrhage cannot be defined by any single criterion. The manifestations of shock are one indication, but the clinical evidence of shock may be lacking in some persons who have lost a great quantity of blood. Values for hemoglobin under 8.0 gm. per 100 ml., and hematocrit values below 30 per cent are good evidence. In some cases, however, supplementation by early transfusions of blood kept the hematocrit above the figure that might have been attained if repair had not been started. In no case in our series was there a trivial or moderate hemorrhage. In fact, large hemorrhages are the rule in bleeding with portal hypertension. In 48 of the 50 patients hematemesis occurred, and in only 2 was blood passed from the bowel alone. All patients in this series met the requirements of a large hemorrhage. In all cases the most recent hemorrhage was the one considered. The site of bleeding and its exact cause are open to question in some patients in whom the presence of esophageal varices cannot be proved. This group cannot be large in any serious study. Doubtful cases, however, are few if hospital records are good and if the rate of post-mortem examinations is high.

Esophageal Varices

Patients with liver disease may have a reduced coagulability of the blood because of a deficiency of prothrombin in the plasma, and, indeed, many who bleed from varices have such a coexisting deficiency. Spontaneous massive bleeding from the upper gastrointestinal tract as the result of a prothrombin deficiency alone is not common in patients with liver disease. Five patients in this group with cirrhosis of the liver did not have esophageal varices demonstrated and proved. In 2 of the 5, roentgenologic studies were not made, and in the other 3, varices were not demonstrated on barium-swallow studies of the esophagus. Nevertheless, these 5 patients conformed to the various clinical and biochemical standards for diagnosis of hepatic cirrhosis. In 45 of the 50 patients with cirrhosis of the liver, therefore, the presence of varices was definitely established by roentgenographic studies of the esophagus with barium, by esophagoscopy or by post-mortem examination in addition in fatal cases. The 5 patients in this group of 50 in whom the presence of esophageal varices was not established have been included in this study because it was believed that all of them bled from varices at the gastroesophageal junction. In any event, these 5 presented the problem of massive gastrointestinal hemorrhage in patients with liver disease probably with portal hypertension. Of the 5 patients 3 were found to have died within a year of discharge from the hospital, and 2 definitely from hemorrhage. Finally, it must be pointed out that exclusion of these cases would only serve to make a gloomy picture worse. It is a recognized fact that the isolated demonstration of esophageal varices by roentgenographic studies or esophagoscopy is not entirely satisfactory. In our series, varices were proved, in one way or another, in 90 per cent of the cases. The very high mortality and the high autopsy rate obtained upon these patients in the hospitals was responsible for the proof of the presence of varices in so many of the patients in this study.

Clinical and Chemical Diagnosis of Liver Disease

In almost all the 50 patients with cirrhosis of the liver the diagnosis was apparently made quite readily from the history and physical examination. There are always a few patients in whom no overt signs of liver disease, such as hepatosplenomegaly, ascites, icterus, spider telangiectasis and abnormal venous circulation, can be found. These represent important diagnostic problems in cases of massive hemorrhage. The laboratory findings are of some help in this group. A few patients whose disease was proved at autopsy had not undergone any chemical tests, having died of massive hemorrhage soon after admission. In other cases there were also deficiencies in the chemical studies. Not all patients had had their prothrombin times estimated, particularly in the earlier years.

The chemical criteria adopted to substantiate the clinical diagnosis of liver disease in this study were as follows. Retention of over 15 per cent of bromsulfalein in forty-five minutes was taken as a lower limit of acceptability for indicating liver disease. Cephalin flocculation values of + + + and + + + + in forty-eight hours were considered abnormal and evidence of liver disease. The prothrombin time was considered to be abnormal when there was a prolongation of four seconds beyond the control level; in cases in which a percentage alone was expressed, a value of less than 45 per cent of normal was taken to substantiate the diagnosis of liver disease when other evidence was present. Reduction of the total serum protein, with a serum albumin value below 3 gm. per 100 ml., was usually found.

Clinical Course

The treatment of these 50 patients with massive hemorrhage from varices and portal hypertension can be divided into three general types, depending to a large extent on the era of their hospitalization. Thus, 28 patients, or slightly over half, were treated without any special technics except general medical care and the replacement of blood, fluids and electrolytes in varying degrees of completeness. These were from the earlier series. The more recent introduction of tamponade of the esophagus by use of balloons delineated another group of 19 patients, and, finally, 4 patients were operated upon during hemorrhage. Surgery may have influenced the outcome in this small group.

Mortality of Hemorrhage

Thirty-three of the 50 patients studied died in the hospital after hemorrhage. The hospital mortality for these patients was therefore 66 per cent. Certain qualifying statements must be made, however, about this high rate. Four patients died after emergency operations performed during the bleeding episode. As far as could be determined the 33 patients could be divided as follows: 20 died of the effects of blood loss alone; and 13 died in coma — 11 while still bleeding, and 2 after hemorrhage had stopped. No patient who went into coma precipitated by hemorrhage survived. This fact is very significant because only about half of the patients (54 per cent) who did not go into coma died. The relation of the severity of liver disease and the fatal effect of hemorrhage is brought out below.

Twenty-nine of the 33 patients who died were studied at post-mortem examination. All 29 were found to have portal cirrhosis and esophageal varices. Twenty-seven had evidence of bleeding from esophageal varices as judged by the presence of blood in the gastrointestinal tract at autopsy. The remaining 2 patients had died in prolonged coma, and although varices were present, no blood was found in the gastrointestinal tract at the time of death. Four patients with fatal hemorrhage were not examined after death. All patients surviving the hemorrhage were followed, and of 17 patients discharged, 7 are known to have died since December 31, 1953. Of these 7, 4 died after hemorrhage, and 1 of liver failure and coma; 2 others were judged by their physicians to have died of heart failure. Only 10 patients, or 20 per cent, were living a year after their hospitalization for hemorrhage. The fact is, then, that 40 patients, or 80 per cent, of this group of 50 patients died within a year of their hemorrhage. It is difficult, therefore, to contradict the fact that hemorrhage from portal hypertension and cirrhosis of the liver is a serious matter. That the liver disease is extremely important in causing the death of these patients cannot be denied, but bleeding often initiates a rapidly fatal course in many persons who would have had an expectation of several years of life.

Factors Influencing Mortality

Age and Sex

The patient's age did not seem to be a factor of great significance in accounting for the high mortality found in this series, but we cannot be at all certain of the age factor alone because of the age distribution in our series. The majority of our patients, 58 per cent, were in the fifth and sixth decades of life, and three quarters were between the ages of forty-one and seventy years. Other things being equal, however, there can be no question that advanced age is a disadvantage to patients with hemorrhage from varices as well as to patients bleeding from gastroduodenal ulcer. The cardiovascular system is taxed by hemorrhage. Of most interest to us regarding age in this group of patients with upper gastrointestinal hemorrhage is the fact that so many of them were fairly young. Forty patients, or 80 per cent of the total, were under sixty years of age, and 31, or 62 per cent, were under fifty. The mortality in patients under fifty years of age was 64 per cent. This is quite a different picture from that seen in bleeding from gastroduodenal ulcer. It presents a challenge of a high order to both the physician and the surgeon for improvement in treatment. A higher survival rate among this group of relatively young people should be possible even though they have cirrhosis of the liver.

There were twice as many males as females, and the mortality was lower in females — 54 per cent, as compared with 72 per cent in males; the significance of this finding is difficult to assess in such a small series, but it is probably true that females have a better prognosis both during hemorrhage and after the elective operation of portacaval shunt.

Influence of Previous Hemorrhage

The question of whether or not the patient who has had one or more hemorrhages before the one under observation has a better outlook for surviving the episode has little significance since the mortality is high in both groups. Actually, we found that 76 per cent of patients suffering a first hemorrhage died; 61 per cent of those who had had one or more hemorrhages died at the time of the hemorrhage in this study. It cannot be inferred that the outlook is good if the patient has sustained one hemorrhage. In fact, the mortality rate seems to rise again significantly when more than two hemorrhages have occurred. There are many factors influencing this aspect of the problem. The important finding — that 76 per cent of patients with a first hemorrhage died — suggests that prevention should be the best solution to this problem; 34 per cent of the patients in this series were in their first episode of bleeding.

The question is often asked, How many patients with esophageal varices never bleed? This question has never been answered. All patients with extrahepatic portal obstruction and varices ultimately bleed, and there is reason to believe that all patients with varices as the result of cirrhosis will bleed if they live long enough and do not succumb to their liver disease first. If this were not true every sizable hospital and clinic would have a substantial number of patients with cirrhosis of the liver and established varices who are being followed. Certainly, no one has presented a group of patients with esophageal varices and cirrhosis of the liver who have lived over a period of years without bleeding. Roentgenologic examination of the esophagus and upper gastrointestinal tract is commonly performed on all patients with cirrhosis. At the Albany Hospital no sizable group of patients with varices who are being followed have not bled. Examination of the hospital records and the diagnostic files of the Department of Radiology has revealed only 4 patients alive with presumed varices, excluding those subjected to portacaval shunts. There seems to be little ground for any contention that the presence of varices in the esophagus and cirrhosis of the liver is common in patients who have not had the complication of bleeding over a long period of observation. There is little justification for the attitude that since many patients with cirrhosis may go on to die of liver disease without hemorrhage, esophageal varices need not be taken seriously when discovered in these patients.

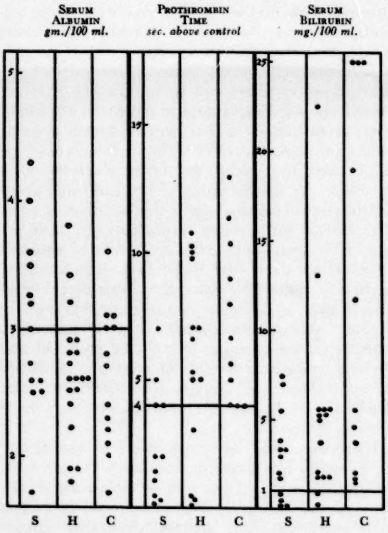

FIGURE 1. *Initial Liver-Function Tests in Patients with Bleeding Esophageal Varices.*

Values for serum albumin, prothrombin time and serum bilirubin are plotted for patients who survived (S), *those who died of hemorrhage* (H) *and those who died in coma after bleeding* (C). *It can be seen that abnormal values were found more commonly among the patients who died. The horizontal lines represent critical levels for each test.*

Status of the Liver Disease

Of the 50 patients with cirrhosis and portal hypertension, 37 had a history pointing to alcohol as the cause. The mortality rate was no greater in this group than in the 13 patients who did not have a substantial history of long-term alcoholism. The influence of the severity of the liver disease on the outcome of a patient with a severe hemorrhage was significant. First of all, the physical findings of advanced liver disease indicating diminished function are ascites and visible jaundice. Hepatic and splenic enlargement are less significant. Icterus is best measured chemically, and, thus, ascites is perhaps the sign most prejudicial to reasonably good liver function. Ascites was present in 40 per cent of patients surviving hemorrhage and in 50 per cent of those who succumbed. This difference is not great. It is true, however, that hemorrhage was probably the terminal event in some patients, and in these, better management of the bleeding episode might have made little difference. The number of such patients cannot be estimated exactly, but it is not the majority of patients. One or more liver-function tests were done at the time of admission in all cases, but a complete battery of tests was not done in each case. The most significant practical tests of liver function are the values for serum albumin, serum bilirubin, prothrombin time, retention of bromsulfalein and, perhaps, cephalin flocculation. In Figure 1 the initial values for 3 of these tests are plotted for individual patients who survived their hemorrhage, died from exsanguination or died in coma initiated by bleeding. Although it is by no means a prerequisite that the patients who died had the poorest liver function of the whole group, it is evident that those who did die, and particularly those who died in coma, had a lower initial serum albumin and were more likely to have a higher serum bilirubin and a more prolonged prothrombin time than the survivors. This finding cannot be interpreted to mean that the patients who died were terminal cases. The significance of a prolonged prothrombin time in the prolongation of bleeding once started is well understood, but prothrombin deficiency is usually correctable in the majority of patients with cirrhosis of the liver. In cases in which it is due to a diminished vitamin K intake, parenteral administration of a suitable vitamin K product may effect a correction. When the liver is incapable of prothrombin formation, whole blood, preferably fresh, or plasma may reduce a prolonged prothrombin time temporarily. It is an

uncommon patient in whom gastrointestinal bleeding of a severe order can be attributed to a prothrombin deficiency alone. There is no doubt, however, that diminished liver function is an important cause of the coma that supervenes in many of these patients (39 per cent of those who died in this series). The mechanism by which coma is produced requires some explanation and will be taken up later.

Esophageal Tamponade

The Sengstaken–Blakemore[1] esophageal tampon first devised by Westphal[2] and Rowntree et al.[3] is a very useful instrument. It will invariably stop a hemorrhage from varices if properly applied. Experience with this tube has demonstrated that the area in which varices are susceptible to hemorrhage is at the esophageal junction since compression exerted by the balloons at this point usually controls hemorrhage. This tube was not used until 1951 in these hospitals. It was applied 28 times in 19 of the patients in this group. The average time that this tube was left in place was thirty-eight hours. Thirteen of these 19 patients, or over two thirds, died. It cannot be said, therefore, that esophageal tamponade saved many lives in spite of the fact that we know that this instrument can stop hemorrhage. This fact brings up the important consideration that stopping the hemorrhage is not the entire problem in these patients. It is important to note that 9 of the 13 patients treated with the tube died in coma rather than of exsanguination alone. The tube probably controlled hemorrhage in some of these patients, but death resulted from metabolic disturbances attributable to their liver disease. The tube has several disadvantages, or rather shortcomings.[4] In the first place, there is some hazard in leaving it in place for a long time. Esophageal ulceration and rupture may occur although this complication is a risk of reasonable acceptance. More importantly, aspiration into the lungs of saliva and other secretions that can no longer be swallowed often produces pneumonitis. It is true that tracheostomy may help keep the tracheobronchial tree clear, but it is not entirely successful and the additional hazard of bleeding at the tracheostomy from a prothrombin deficiency may defeat this maneuver. Finally, removal of this tube may be followed by renewal of bleeding since a secure thrombosis in the varix is not always formed. It is a problem to decide on the proper time for removing the Sengstaken–Blakemore tube. Seventy-two hours of tamponade is usually tolerated fairly well, but patients vary a great deal in their tolerance of this procedure.

Surgery during Hemorrhage

Four of the 33 patients who died were subjected to surgery. One died after splenectomy was performed during hemorrhage from varices. Another died of bleeding from varices during an attempted portacaval shunt. There were 2 patients who died of liver failure a month or more after emergency surgery had been performed during a bleeding episode. One of these had an emergency transthoracic ligation of esophageal varices, and the second an emergency portacaval shunt. If these 4 patients are excluded from the 33 who died after hemorrhage, the mortality for patients not interfered with surgically is still 58 per cent. It is not reasonable to believe, however, that all 4 patients would have lived if not operated upon since the situation seemed desperate in each case. We do not have sufficient experience as yet to judge for ourselves whether immediate surgery on patients bleeding from esophageal varices will be life saving. The results obtained by Crile[5] and Linton[6] indicate that transthoracic esophagotomy and ligation of the varices can be done with a reasonable mortality and is efficient in stopping bleeding. As Linton points out, these patients must be operated upon early, soon after the initial hemorrhage. Early operation may well be the solution for some of them. Again, it must be pointed out that patients who have gone into coma present a problem of greater magnitude than that of exsanguination alone. Operative ligation of the varices is not the whole answer for the group in coma. Since coma was the secondary cause of death in over a third of the patients in this series, a discussion of the mechanisms involved in coma is pertinent to an understanding of the problem of treatment once coma has appeared.

Mechanism of Coma in Hemorrhage with Liver Disease

Experimental studies in dogs shed some light on the etiology of hepatic coma. It has been proved that reduced blood flow to the liver in dogs, particularly to the point of total ischemia, may result in death by a mechanism resulting from liver hypoxia or anoxia.[7] Diminished liver blood flow and diminished oxygen supply apparently encourage the growth of anaerobes, particularly clostridia, which are already present in the dog's liver.[8] The work of Fine and his collaborators[9,10] has shown repeatedly that the liver is implicated in irreversible shock and that toxins elaborated by bacteria are in all probability an important cause of the peripheral vascular failure and sustained hypotension in dogs subjected to shock experiments. The studies of Raffucci and Wangensteen[11] are especially conclusive in showing that the dog's liver will not stand hypoxia. In our laboratory, experiments on transplantation of the liver in dogs demonstrate conclusively that a liver deprived of blood flow for over thirty minutes cannot be successfully transplanted even if the donor animal has been prepared by a protective course of antibiotic therapy.[12] The work of Rappaport et al.[7]

goes on to show that one can easily produce coma and death in dogs by eliminating the hepatic vascular inflow. Ligation of the hepatic arteries and diversion of the portal blood into the vena cava by an Eck fistula caused death in a very high percentage of dogs so altered. The liver may show widespread necrosis of the lytic type in animals that succumb in coma after devascularization. There is no question, therefore, that in the dog reduced liver blood flow and anoxia easily produce severe liver damage and that coma can result from severe local changes in the liver that are often irreversible.[13-15] Severe liver ischemia produced by ligation of the hepatic arteries in the human subject may also result in death even though human livers are, as a rule, sterile on routine culture.[16] When the human liver is rendered ischemic, however, bacteria may invade it and give rise to a train of events not unlike that seen in dogs.[17] Preliminary treatment with a course of wide-spectrum antibiotics often protects both animals and human subjects against death from liver autolysis.[18-21] Relatively short periods of ischemia, therefore, may encourage bacterial growth and toxin production, which can conceivably be a factor in the death of patients with liver disease.[22] It is also true beyond doubt that massive necrosis of the liver without invoking any bacterial intervention produces coma of hepatic origin. Coma resulting from anemic infarction of the liver is an uncommon clinical syndrome in man, however.

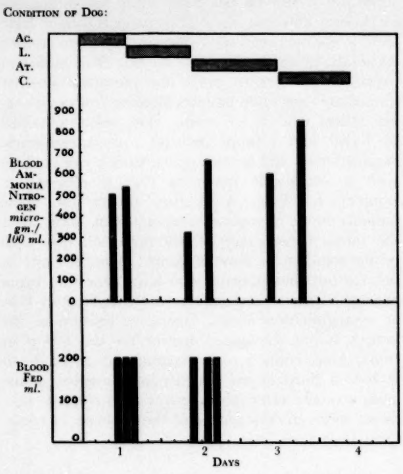

Figure 2. *Ammonia Intoxication from Feeding of Blood to an Eck-Fistula Dog (Ac. = Active, L. = Lethargic, At. = Atoxic, and C = Comatose).*

The blood ammonia nitrogen rises, and the animal ultimately dies of "blood intoxication."

The considerations just reviewed do not offer a convincing explanation of the mechanism of coma and death after hemorrhage from esophageal varices when viewed in the light of clinical experience. These patients with hemorrhage are seldom allowed to exist for long periods with hypotension from exsanguination because of the practice of early blood replacement. Hypotension and liver anoxia are probably not the cause of coma in this syndrome. Examination of the livers of patients in our series who died in coma showed only chronic liver disease, with no evidence of a superimposed recent necrosis or lytic process that might be expected to follow ischemia and anoxia. Increasing information of abnormalities of nitrogen and ammonia metabolism in severe liver disease indicate to us a far more plausible mechanism of coma genesis. The observations of Riddell, Kopple and McDermott[24] have shown the relation between high blood ammonia values and the so-called meat-intoxication syndrome in dogs. High ammonia values artificially induced by nitrogen feeding in human patients with cirrhosis of the liver have been correlated with neurologic changes to the point of coma by Phillips et al.[25] Blood is certainly a substance high in nitrogen (9 to 12 gm. of nitrogen per liter) and quite capable of producing a syndrome similar to meat intoxication in human subjects with severe liver disease, as McDermott and his associates[26] have also pointed out.

It is more probable that hepatic coma is initiated by the absorption of large amounts of digested blood in the intestine.[27] It is not uncommon to have to administer 4000 or 5000 ml. of blood to bleeding patients to raise and maintain the blood pressure and hematocrit at a reasonable level during the first forty-eight to seventy-two hours when, at the same time, a much smaller quantity of blood has been vomited or dejected. The diseased liver cannot metabolize normally the nitrogenous products resulting from the digestion and absorption of the blood in the gastrointestinal tract so that high values for blood ammonia nitrogen follow hemorrhage from varices in severe cirrhosis. The situation is quite analogous to the meat-intoxication syndrome that can be induced by meat feeding in dogs with complete portal-blood diversion into the vena cava. In this experimental syndrome, ammonia intoxication results from the direct diversion of portal blood that has a high ammonia value into the systemic venous system in which case the blood has not been subjected to the liver's function in nitrogen metabolism.

Figure 2 shows the effect of feeding blood to a dog with an Eck fistula. The values for blood ammonia nitrogen rose consistently in this animal to 900 microgm. per 100 ml. when death supervened. This finding has been constant in a series of experiments conducted by one of us.[28]

This concept that coma is induced by the absorption of digested blood in the intestine can be applied

to treatment. No one questions the importance of stopping the bleeding from the varices as an essential of treatment, but the importance of cleaning the blood out of the gastrointestinal tract as soon as possible and as completely as possible has been overlooked as an equally essential step. Blood can be removed by aspiration from the stomach, but purgatives and enemas are required to remove the larger and more significantly located volume of blood that is in the intestine. In addition to the use of the Sengstaken–Blakemore tube for stopping bleeding from the varices, the intestines should be emptied by the administration of purgatives through the tamponade tube at frequent intervals, and enemas should also be given. These measures must be preceded by stabilization of the blood pressure by adequate replacement of blood.

It is fairly clear, therefore, that the coma that accompanies hemorrhage into the gastrointestinal tract is not a hepatic coma of the type that is initiated by and follows liver necrosis. There are no acute liver lesions in these patients that can be correlated with coma. Their livers look about the same after death from coma as they would if they had died from another cause. The coma of hemorrhage is more probably an intoxication, as described above. It probably should not be called hepatic coma. Perhaps ammonia intoxication better describes this metabolic derangement. The prevention of this coma is often possible but has been neglected in the present-day management of bleeding from varices.

Discussion

Prevention of Bleeding from Varices

Other studies as well as the present one have shown that the mortality of hemorrhage from esophageal varices and cirrhosis of the liver is very high.[29-32] The fact that the first hemorrhage is often fatal is regrettable; only a quarter of such patients survive. But high mortality is not entirely the result of an inability to arrest bleeding. The fact that the cirrhotic, diseased liver with poor function is inadequate to the task of metabolizing the large amount of nitrogenous products that come from the digestion and absorption of blood in the intestine is almost equally important in the whole picture. Surely, the facts recommend a program of prevention of the hemorrhage from varices since it is difficult to bring these patients through a bleeding episode. There is no medical regimen that will prevent hemorrhage from varices. Improvement in the patient's general condition and liver function is not invariably accompanied by a reduction of portal tension. Unfortunately, portal pressure may increase as the liver function improves. Healing in the cirrhotic liver and regeneration of the liver lobules may increase portal-vein obstruction.[33] This fact is not universally appreciated by physicians. Not a few patients have a sudden fatal hemorrhage at a time when they are improving and have been established on a good regimen after much effort on the part of the patient and physician.

Shunting of the blood from the portal to the systemic venous system by the use of a large-vein anastomosis, either a direct portacaval or a splenorenal shunt, has proved to be of great benefit in patients who have survived one or more hemorrhages. There is adequate testimony that these shunts prevent lethal hemorrhages by reducing the relatively high portal-vein pressure in the esophageal varices.[34-37] There is an understandable reluctance on the part of physicians to subject to a very major operative procedure patients with liver disease who are doing seemingly well. Portacaval shunts are difficult operations but cannot any longer be classed as formidable. The mortality of these operations has consistently decreased over the years so that it now ranges from 10 to 15 per cent in experienced hands. If shunts are recommended for patients who have had one or more hemorrhages, why are they not equally desirable for protecting patients from a first hemorrhage, which is often fatal? It seems to us that there could be two objections to the prophylactic employment of portacaval shunts in patients who have proved esophageal varices. A prohibitive operative mortality of shunt procedures would be a reasonable deterrent to its recommendation, but the mortality is not high.[38] Secondly, if there were good reason to believe that many patients live for years with varices and do not bleed from them, this would be another valid reason against prophylactic shunts. There is no evidence in the literature on cirrhosis of the liver that any sizable series of patients with portal hypertension and esophageal varices have not bled. The occasional observation that varices disappear in patients[39] is not pertinent to this problem, nor are such observations entirely reliable. Roentgenologists and endoscopists will attest to the fact that the diagnosis of varices may be very difficult and open to question.

The fact that all patients with cirrhosis of the liver do not die of hemorrhage or do not even bleed is not pertinent to the problem either. In the Albany Hospital the figure for bleeding among patients with cirrhosis of the liver is approximately 30 per cent. Many patients with cirrhosis have no evidence of varices, and the majority die of liver failure and causes other than hemorrhage. It is the patient who is discovered to have varices that needs consideration for a portacaval shunt. It seems reasonable that he should be considered for operation if he is an acceptable candidate as defined by the same criteria that apply to patients who have previously bled. Although it is true that a direct comparison between the mortality rates of bleeding and the operative mortality rates of portacaval shunts is not equitable, the evidence is overwhelming that

the risk to life of a first hemorrhage is so great in a sizable group of patients that a "preventive shunt" could be considered in each patient with demonstrated esophageal varices. Patients must always be evaluated individually, for many factors are involved.

Treatment of Hemorrhage from Esophageal Varices

In addition to the question of prevention of hemorrhage discussed above, what information has been obtained from this study that can be applied to the challenging problem of reducing the mortality among these patients once hemorrhage has appeared? The fact that approximately a third of the patients who died in this series did so after going into coma offers a challenge in treatment. It also should be recalled that all patients who went into coma after a hemorrhage died. Without operative intervention it is quite possible that better results can be obtained in the future than in the past. A better understanding of the cause of coma and its prevention is perhaps the most important item upon which attention should be concentrated. A three-point program for the treatment of patients bleeding from varices with liver disease that considers all aspects of the problem can be evolved.

Stopping the hemorrhage is the first step, the Sengstaken–Blakemore esophageal balloon tampon being used in addition to the usual blood-loss replacement and treatment of shock. This tube should be passed immediately in all suspected cases of bleeding from varices. When it is properly applied hemorrhage will cease, as evidenced by the absence of blood in the gastric aspiration. Too often this tube is not used early; it is a diagnostic instrument as well as a therapeutic one, since, if it stops a hemorrhage promptly, the source of bleeding is anatomically located, and in all probability the bleeding is from varices at the esophagogastric junction. Too often the tube is not passed soon enough, because it is believed that the patient has already stopped bleeding after his initial emesis. Particularly is this true if his blood pressure is not at shock level. He continues to bleed and does not vomit again until his stomach is full. Valuable time is lost in stopping hemorrhage and the fact that bleeding is continuing is masked by the concurrent blood-replacement therapy.

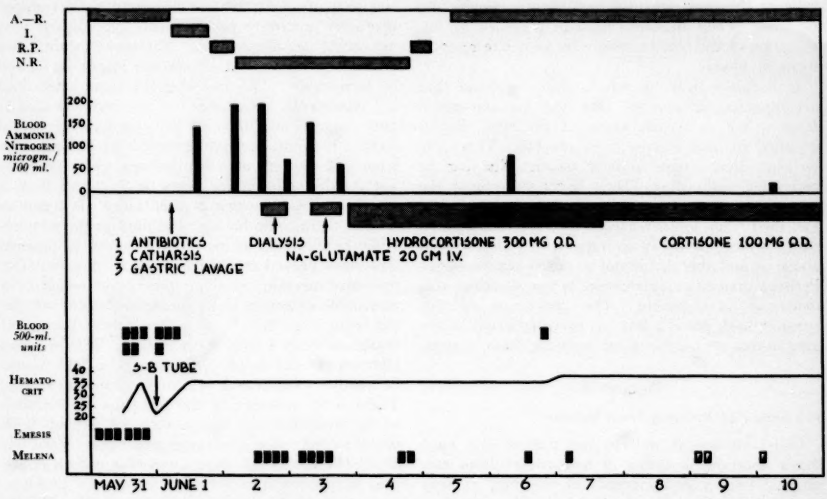

FIGURE 3. *Course and Treatment of a Patient with Massive Hemorrhage from Esophageal Varices (A.—R. = Alert and Rational, I. = Irrational, R.P. = Responding Only to Pain, and N.R. = Not Responding at All). Note the effect on the blood ammonia nitrogen of hemodialysis, administration of sodium glutamate and evacuation of blood from the intestine.*

Evacuation of blood from the entire gastrointestinal tract is the second most important step in the treatment of patients with esophageal varices and bleeding. This can be accomplished by milk of magnesia fed hourly through the tube combined with enemas or colonic irrigations. Other laxatives or purgatives may be used. Evidence that hemorrhage has been arrested by the tube can be obtained sooner if the stomach has been washed out. The

blood pressure should be stable and above shock levels before the evacuation of the gastrointestinal tract is carried out, and caution must be exercised during the whole procedure.

Reparative and detoxifying therapy can be applied as the third therapeutic attack. The administration of blood, vitamins, especially vitamin K, and concentrated glucose solution are established as useful in improving liver function. The plasma electrolytes must be measured, and any deficiencies corrected.

Values for blood ammonia should be obtained immediately upon admission and repeated twice daily. A rise in blood ammonia nitrogen will be found in the majority of patients who bleed massively with cirrhosis of the liver, and this estimation is of prognostic value in determining the patient's ability to metabolize his digested blood. If the blood ammonia continues to rise, coma will often ensue. The effectiveness of evacuation of blood from the gastrointestinal tract can also be estimated by serial determinations of blood ammonia nitrogen.

Finally, attempts should be made to reduce the concentration of ammonia in the patient's blood. The administration of glutamic acid in the form of sodium L glutamate has been shown to reduce blood ammonia and to restore consciousness in some patients in coma.[40] This drug is in the experimental phase. Corticoid therapy has been used empirically and in selected cases seems to be of value.[41,42] The mechanism of its action is not known. Work in progress at the Albany Hospital on hemodialysis has shown that ammonia nitrogen can be removed from the blood by the use of the Kolff artificial kidney.[43] This technic has been applied to patients and is presently under study. It may be of value especially in patients with very high blood ammonia values. Wide-spectrum antibiotics should probably be given also since sterilization of the bowel has been shown to reduce ammonia production.[44]

In Figure 3 a representation has been made of the application of this three-point program to a patient with cirrhosis of the liver who bled and became comatose. This patient was intubated, purged and dialyzed and received both sodium L glutamate and finally cortisone, with recovery. Oxytetracycline was also administered. No individual item of therapy is held responsible for his recovery. It can be seen from the graph, however, that hemodialysis rapidly reduced his blood ammonia value for a time. It also appears that sodium L glutamate administration was followed by a reduction in the value for blood ammonia. The effectiveness of purgation is shown by the number of bloody evacuations recorded. It is most significant that bleeding had been controlled by the Sengstaken–Blakemore tube and that the intestinal tract was emptied of the large amount of blood that had accumulated in it. The volume of blood necessary to establish an adequate hematocrit reading is an index of the bleeding that had occurred. The management of the bleeding episode in this patient is shown to point out the importance of the treatment of ammonia intoxication, from which so many patients die.

Summary and Conclusions

The life history of patients with cirrhosis of the liver who bleed massively from the upper gastrointestinal tract is reviewed.

In a series of 50 consecutive patients with cirrhosis of the liver and portal hypertension who bled, 33, or 66 per cent, died in the hospital, and 80 per cent of this group died within a year of their hemorrhage.

Seventy-six per cent of patients with a first hemorrhage died.

Thirty-four per cent of the patients who died after hemorrhage died in coma.

The mechanism of the production of coma in these patients is discussed.

A program of treatment for patients bleeding with cirrhosis of the liver must take into consideration that coma may be preventable, and can be better treated if attention is paid to certain details that are outlined.

Finally, arguments are presented that portacaval shunts should be performed in patients with cirrhosis of the liver and esophageal varices before they bleed.

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BRONCHOGENIC CARCINOMA IN PERSONS UNDER FORTY YEARS OF AGE*

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BRONCHOGENIC carcinoma is generally considered a disease that affects predominantly middle-aged and elderly men. Younger persons, however, may be affected, and it is important that the clinician consider it as a possible diagnosis in any person, regardless of age or sex, whose thoracic roentgenogram discloses an abnormal pulmonary shadow.

The present study was undertaken to review the experience at the Mayo Clinic with bronchogenic carcinoma occurring both in males and in females under forty years of age. Where indicated, comparisons are made between the findings in this group of cases and those of Kirklin and his associates,[1] who reported on all patients having bronchogenic carcinomas seen at the Clinic during the years 1943 to 1949. Many of the cases in that study are, of course, included here.

MATERIAL AND METHODS

The records of all patients under forty years of age in whom the diagnosis of primary bronchogenic carcinoma had been made at the Clinic in the years 1943 through 1954 were reviewed. Patients who had previously received definitive treatment elsewhere for carcinoma of the lung were excluded. All cases in which there was any possibility, however slight, that the malignant lesion of the lung was metastatic were discarded. The following cases were included in the study: those in which tissue from the primary lesion was available for histologic examination; those in which the history, physical findings and roentgenographic studies warranted a diagnosis of primary bronchogenic carcinoma, and results of cytologic examination of sputum or bronchial secretions were positive for malignant cells; and those in which the diagnosis of inoperable primary bronchogenic carcinoma, made on the basis of clinical and roentgenographic findings, was supported by histologic examination of tissue removed from distant metastatic foci, such as supraclavicular lymph nodes.

The slide preparations for cytologic examination of sputum and bronchial secretions were available for re-examination in 8 of the 9 cases in which the diagnosis was proved by this method. Histologic preparations of neoplastic tissue were re-examined in 40 of the remaining 42 cases.

On the basis of the criteria described, there were 51 cases of primary bronchogenic carcinoma among patients under forty years of age.

CLINICAL FINDINGS IN 51 CASES OF PRIMARY BRONCHOGENIC CARCINOMA

Age and Sex Distribution

Thirty-nine patients were men, and 12 were women (Table 1). The ratio of men to women (3.25:1) was appreciably lower than that reported for bronchogenic carcinoma in all ages, which varies from 5:1 to 10:1. Three patients were under thirty years of age, but no patient was less than twenty-four years old.

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Symptomatology

Two patients were entirely asymptomatic. In the remaining 49 the duration of symptoms, before the diagnosis was established, varied from 2 weeks to twelve months, the average being four and three-tenths months. In reports on bronchogenic carcinoma for all ages, Lindskog and Bloomer[2] and Tinney[3] found the average duration of symptoms before diagnosis to be seven and nine-tenths and eight and five-tenths months, respectively.

The various symptoms and the number of cases in which each occurred are listed in Table 2. Forty-three patients had symptoms referable to the respiratory tract. The most frequent were cough and hemoptysis. Twelve had symptoms referable to distant metastasis, and 11 had symptoms referable to involvement by direct extension of structures adjacent to the primary lesion. On the basis of symptoms alone, however, 16 patients (31 per cent) gave evidence of inoperability by reason of distant or local spread.

The frequency of symptoms attributed to involvement of the larger bronchi — namely, cough and hemoptysis — in this study is considerably higher than that reported by Anderson and his associates,[4] and closely approximates the incidence of such symptoms in bronchogenic carcinoma for all ages reported by Tinney[3] and by Gibbon et al.[5] and Ochsner and his co-workers.[6]

Findings on Physical Examination

Physical examination gave entirely negative results in 11 patients. The various significant physical findings and the number of cases in which each occurred are shown in Table 3. Physical examination alone gave evidence of inoperability in 20 (39 per cent) of the 51 patients, the most frequent sign being the presence of enlarged supraclavicular lymph nodes. This high rate of apparent inoperability when the patient was first seen does not differ significantly from that reported in bronchogenic carcinoma for all ages by Gibbon et al.,[5] Ochsner et al.[6] and Ariel and his associates.[7]

TABLE 1. *Age and Sex Distribution of 51 Patients under Forty Years of Age.*

AGE	NO. OF MEN	NO. OF WOMEN	TOTALS
yr.			
24	1	0	1 (2.0%)
25-29	0	2	2 (3.9%)
30-34	12	6	18 (35.3%)
35-39	26	4	30 (58.8%)
Totals	39	12	51 (100.0%)

DIAGNOSIS

Bronchoscopy was carried out in 32 patients, and in 21 the diagnosis was established by bronchoscopic visualization and biopsy of the lesion. In 5 of these 21 the lesion was considered inoperable because of involvement of the carina or trachea or both. In 10 patients the diagnosis of primary bronchogenic carcinoma was made on the basis of clinical and roentgenographic findings and on histologic examination of tissue removed at biopsy from distant metastatic foci. In 9 patients the diagnosis was proved by the finding of malignant cells on cytologic examination of sputum or bronchial secretions; in 8 the diagnosis was established at surgical exploration of the thorax. In the remaining 3 the diagnosis was proved at autopsy.

TABLE 2. *Symptoms.*

SYMPTOM	NO. OF PATIENTS	PERCENTAGE
Referable to primary lesion in lung:		
Cough	40	78
Hemoptysis	32	63
Dyspnea on exertion	25	49
Thoracic pain	24	47
Fever, chills & night sweats	17	33
Wheeze	4	8
Referable to distant spread:		
Severe headaches, with symptoms referable to central nervous system*	6	12
Swelling in neck	3	6
Cutaneous lesions	2	4
Jaundice	1	2
Referable to local spread of primary lesion:		
Pain in shoulder, neck & arm	8	16
Hoarseness	2	4
Dysphagia	1	2
Systemic symptoms:		
Significant loss of weight	24	47
Malaise, anorexia, weakness & fatigue	15	29
Pain or swelling in multiple joints	2	4
Recurrent severe headaches	2	4

*Symptoms referable to central nervous system included 2 or more of following: nausea & vomiting; vertigo; visual disturbance; & ataxia. Headache alone not considered evidence of cerebral metastasis.

PATHOLOGICAL ASPECTS

According to the microscopical classification now in use at the Mayo Clinic, primary bronchogenic carcinoma is divided into four types: squamous-cell carcinoma; adenocarcinoma; small-cell carcinoma; and large-cell carcinoma. Definite microscopical criteria are required for classification in each of these types and have been described previously by McDonald and his associates.[8] The frequency and sex distribution of each cell type in the 51 cases studied are listed in Table 4. For comparison, the findings of Kirklin et al.[1] for patients of all ages are also listed.

The small number of squamous-cell carcinomas

in this group of young patients (7.8 per cent) is in striking contrast to the frequency in patients of all ages (33.7 per cent). The incidence of squamous-cell carcinoma was less frequent in this series of young patients than in that reported by Anderson and his associates,[4] who found 5 such lesions (16.6 per cent) among 30 in a study confined to males less than forty

TABLE 3. *Significant Physical Findings.*

SIGN		NO. OF PATIENTS	PERCENTAGE
Pulmonary signs*		32	63
Enlarged lymph nodes		15	29
Unilateral supraclavicular	10		
Unilateral axillary	3		
Unilateral supraclavicular & axillary	1		
Bilateral supraclavicular & cervical	1		
Paralysis of left vocal cord		3	6
Clubbing of fingers & toes		3	6
Obstruction of superior vena cava		2	4
Cutaneous lesions		2	4
Ataxia, dysarthria, tremor		2	4
Unilateral proptosis		1	2
Abdominal mass & jaundice		1	2

*Pulmonary signs included diminished resonance to dullness on percussion, diminished intensity or absence of breath sounds, diminished respiratory excursion of thoracic wall & diaphragm, rales & rhonchi; 12 patients had signs of pleural effusion.

years of age. The same investigators analyzed reports of histologically proved bronchogenic carcinoma occurring in children less than fifteen years of age and found a total of 16 cases, none of which were of the squamous-cell type. Beeler and Irey[9] reported, in their study of 50 cases of bronchogenic carcinoma, that autopsy disclosed only 1 squamous-cell lesion among 7 patients under forty years of age. These

TABLE 4. *Comparison of Frequency of Cell Type of Bronchogenic Carcinomas among Patients under Forty Years of Age and Those of All Ages.*

TYPE OF LESION	PATIENTS UNDER 40			PATIENTS OF ALL AGES
	MEN	WOMEN	TOTALS	
Adenocarcinoma	14	5	19(37.3%)	97(12.6%)
Large cell	11	3	14(27.5%)	291(37.9%)
Small cell	9	3	12(23.5%)	121(15.8%)
Squamous cell	4	0	4(7.8%)	258(33.7%)
Unclassified	1	1	2(3.9%)	
Totals	39	12	51(100.0%)	767(100.0%)

figures reveal a much lower frequency of squamous-cell lesions in primary bronchogenic carcinoma in patients under forty than in older persons.

Relation of Location of Lesion to Type of Cell

In some cases the location of the lesion was determined by multiple examinations — for example, roentgenograms of the thorax, bronchoscopic examination, exploration of the thorax and examination of the specimen removed at operation or autopsy. On the basis of the most reliable evidence at hand in each case the 51 lesions were classed as "hilar" or "peripheral" (Table 5). Thirty-six (71 per cent) were located in the region of the hilus of the lung, and 15 (29 per cent) in the periphery. As would be expected, 14 of the 15 peripheral lesions were of the adenocarcinoma and large-cell types. It is notable that the 36 hilar lesions were made up equally of adenocarcinomas, small-cell carcinomas and large-cell carcinomas. Involvement of the larger bronchi by lesions of the adenocarcinoma type is generally considered to be less frequent than noted here.

Our findings pertaining to the relative frequency of hilar and peripheral malignant lesions are the reverse of those of Anderson and his associates,[4] who stated that only 23 per cent of the lesions in their series were located in the hilar region whereas 77 per cent were peripherally located. They explained the relative infrequency of bronchial symptoms noted by the preponderance of circumscribed lesions toward the periphery of the lung away from the larger bronchi. Our figures, however, are more in agreement with the relative distribution of hilar and peripherally located malignant lesions in bronchogenic

TABLE 5. *Location and Cell Type of the Primary Lesion.*

LOCATION	ADENO-CARCINOMAS	SMALL-CELL CARCINOMAS	LARGE-CELL CARCINOMAS	SQUAMOUS-CELL CARCINOMAS	UNCLASSIFIED LESIONS	TOTALS
Hilar	10	11	9	4	2	36
Peripheral	9	1	5	0	0	15
Totals	19	12	14	4	2	51

carcinoma among persons of all ages as reported by Doll and Hill[10] and others.[6,9]

TREATMENT AND RESULTS

In 32 (63 per cent) of the 51 patients the lesions were considered inoperable for reasons listed in Table 6. The remaining 19 patients were considered to have operable lesions. Thoracotomy was carried out in all these cases, giving an exploration rate of 37.3 per cent. Resection with a view to cure was possible in 9 patients, giving a rate of curative resection of 47 per cent of patients explored, or 17.7 per cent of the entire 51 cases. Resection with a view to palliation was possible in 4, or 21 per cent, of the patients explored. The lesions were nonresectable in 6 patients, or 32 per cent explored. These findings are compared with the experience at the clinic in patients of all ages (Table 7). The differences are not striking although a slightly higher rate of exploration and resection rate with hope of cure is noted when patients of all ages are considered than when the group is restricted to younger people.

Of the 9 patients who underwent curative pneumonectomy 1 patient is living and apparently well

three and a half years after operation. Of the remaining 8 patients, 7 died within five to thirteen months of operation, and 1, who died four years after operation, was shown at autopsy to have died of bronchogenic carcinoma.

TABLE 6. *Reasons for Inoperability in 32 Cases of Primary Bronchogenic Carcinoma.*

REASON FOR INOPERABILITY	NO. OF PATIENTS
Proved extrathoracic nodal metastasis	10
Extent of lesion as seen at bronchoscopy	5
Cytologically positive pleural fluid	3
Paralysis of vocal cord (presumed due to involvement of laryngeal nerve)	3
Proved cerebral metastasis	2
Proved cutaneous metastasis	2
Obstruction of superior vena cava	2
Cerebral metastasis (suspected clinically)	2
Cerebral and bony metastasis (suspected clinically)	1*
Metastasis throughout both lung fields (suspected clinically)	1
Bronchogenic carcinoma, small-cell type, with massive pleural effusion	1
Total	32

*Proved subsequently at autopsy.

As already noted, exploratory operations were carried out in 37.3 per cent of 51 patients. There were no operative deaths. Anderson and his associates[4] reported an exploration rate of 47 per cent in their series of males under forty years of age. Exploration rates for primary bronchogenic carcinoma among patients of all ages have been variously reported as 71 per cent by Gibbon and his co-workers,[5] 54 per cent by Ochsner et al.,[6] 48 per cent by Kirklin and his associates[1] and 25 per cent by Bignall.[11] The resectability-for-cure rate in this series was 17.7 per cent of all patients, or 47 per cent of those explored. Anderson et al.[4] described a similar rate of 17 per cent of all patients, or 38 per cent of those explored. Kirklin and his co-workers,[1] who reported on bronchogenic carcinoma for patients of all ages seen at the Mayo Clinic, gave a resectability-for-cure rate of 24 per cent of all patients, or 50 per cent of those explored, and Ochsner and his associates[6] figures of 10.5 per cent and 19.5 per cent respectively. Ariel et al.[7] reported resectability rates of 4.6 per cent and 34 per cent. Sellors[12] has recently reported (1955) a curative resection rate of 64.7 per cent of patients explored.

TABLE 7. *Operability and Resectability among Patients of All Ages.*

STATUS OF PATIENT	PATIENTS UNDER 40	PATIENTS OF ALL AGES
Resection for cure	9(17.7%)	184(24.0%)
Resection for palliation	4(7.8%)	38(5.0%)
Lesion unresectable at operation	6(11.8%)	147(19.2%)
No thoracotomy	32(62.7%)	398(51.8%)
Totals	51(100.0%)	767(100.0%)

Although the operability and resectability rates for bronchogenic carcinoma in people under forty years of age and those for patients of all ages are not strikingly different, the survival rate is much lower in younger patients. In this study there were no five-year survivals among the 9 patients who underwent curative resection. At the time of our study only 1 patient still survives who may live for five years. This is to be contrasted with five-year-survival rates in bronchogenic carcinoma for patients of all ages after curative resection of 37 per cent at the Clinic, as reported by Kirklin and his associates,[1] of 20 to 25 per cent after pneumonectomy and lobectomy, respectively, by Churchill et al.,[13] of 38 per cent by Ochsner and his co-workers,[6] of 22 per cent by Gibbon and his associates[5] and of 20 per cent by Sellors.[12]

Relation of Cell Type to Operability, Resectability and Survival

The relation of cell type of the lesion to operability and resectability is shown in Table 8. None of the 12 small-cell carcinomas was resectable with a view to cure. The resectability rate for large-cell lesions was surprisingly high, since slightly more than a third were resectable with a view to cure. On the other hand, the resectability rate for adenocarcinomas in this study was surprisingly low, being less than half that of the large-cell lesions, and differs greatly from the relatively high rate reported by Kirklin and his associates.[1] In this study 1 of 4 squamous-cell lesions was resectable with a view to cure; this number is

TABLE 8. *Cell Type, Operability and Resectability.*

STATUS OF PATIENT	PATIENTS WITH SQUAMOUS-CELL CARCINOMA	PATIENTS WITH ADENOCARCINOMA	PATIENTS WITH SMALL-CELL CARCINOMA	PATIENTS WITH LARGE-CELL CARCINOMA	PATIENTS WITH UNCLASSIFIED TYPE	TOTALS
Resection for cure	1(25.0%)	3(15.8%)	0(0%)	5(35.7%)	0(0%)	9(17.7%)
Resection for palliation	0(0%)	2(10.5%)	2(16.7%)	0(0%)	0(0%)	4(7.8%)
Lesion nonresectable at operation	0(0%)	1(5.3%)	1(8.3%)	4(28.6%)	0(0%)	6(11.8%)
No thoracotomy	3(75.0%)	13(68.4%)	9(75.0%)	5(35.7%)	2(100%)	32(62.7%)
Totals	4(100.0%)	19(100.0%)	12(100.0%)	14(100.0%)	2(100%)	51(100.0%)

too small for any evaluation of resectability rate for lesions of this cell type alone.

None of the 9 patients in this study who underwent curative resection, regardless of cell type of the lesions, have survived for five years. It is recognized that the five-year-survival rates after curative resection in bronchogenic carcinoma for all ages are relatively high for squamous-cell lesions; they are lowest for the small-cell lesions. Although the number of patients undergoing resection in this study is too small for calculation of survival periods for each cell type, it should be mentioned that the 1 patient still living after curative resection had a squamous-cell carcinoma. The patient who lived for four years after curative resection had a large-cell carcinoma.

Involvement of Hilar Lymph Nodes and Extent of Lesion in Explored Cases

Five of the 10 patients in whom the lesion was nonresectable, or in whom only palliative resection could be carried out, had gross involvement of multiple hilar and mediastinal lymph nodes. Seeding of the pleura or pericardium, or both, was present in 3 patients. Additional evidence of extensive spread of the lesion included fixation to the thoracic wall, aorta and vertebral column and involvement of the brachial plexus.

In 5 of the 9 patients in whom curative resection was carried out, multiple hilar lymph nodes were involved. Intrapericardial dissection and en bloc removal of hilar and mediastinal nodes were done in 4 of these 5 patients; all 5 are known to have died within five to thirteen months of operation. On examination of the resected specimens 2 patients were found to have involvement by direct extension of one hilar node; 1 of these still survives and is apparently well three and a half years after operation.

In the remaining 2 patients of the 9 who underwent curative resection, lymph-node involvement was not found on examination of the resected specimens, but there was pleural involvement in 1. The patient with pleural involvement lived for four years; the other patient died eight months after operation.

Discussion

It is the opinion of many physicians that, in general, malignant lesions occurring in young people grow and spread more rapidly than those occurring in the older age groups. Anderson and his coworkers[4] have stated that primary bronchogenic carcinoma in young people behaves similarly. We agree with these workers, but, on the basis of our data, we cannot attribute this accelerated course to variations in occurrence of the cell types. Although squamous-cell lesions are infrequent in this age group and rare in females, it seems to us that bronchogenic malignant lesions, whether differentiated or undifferentiated, characteristically grow and metastasize more rapidly in youth than in old age.

In contradistinction to the findings reported by Anderson and his associates[4] the symptoms of the disease and the relative frequency of hilar and peripherally located lesions are essentially the same in people less than forty years of age as in older people. Bronchoscopic examination, therefore, is of considerable value in establishing the diagnosis; positive results of biopsy were obtained in two thirds of the patients who underwent bronchoscopy in our study. In this age group, however, our data suggest that involvement of the larger bronchi by lesions of the adenocarcinoma type is more frequent than in older persons.

We have not noted striking differences for operability and resectability rates in people under forty years of age as compared with bronchogenic carcinoma in patients of all ages. Our data, necessarily compiled from a small number of cases, indicate, however, that the number of survivals after resection is definitely lower in these younger patients than in older persons. In this study there were no five-year survivals, and only 1 patient who could conceivably have become a five-year survival after curative resection. Anderson and his co-workers[4] have stated that resection was not known to be curative in any case in their study of bronchogenic carcinoma in 30 males under the age of forty years.

Summary and Conclusions

The findings at the Mayo Clinic in 51 cases of primary bronchogenic carcinoma in patients under forty years of age are presented and compared with those for bronchogenic carcinoma in people of all ages. Bronchogenic carcinoma is a more rapidly fatal disease in patients of this age than in older persons. The chances of cure or even long survival are small and are practically nonexistent when metastasis to hilar lymph nodes has occurred. With the possible exception of squamous-cell lesions, which are infrequent in males and rare in females under forty years of age, the cell type does not appear to have prognostic significance in bronchogenic carcinoma in this age group.

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USE OF PIPRADROL IN OBSTETRICS AND GYNECOLOGY*

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EXTENSIVE clinical investigation utilizing pipradrol (alpha-[2-piperidyl] benzhydrol hydrochloride), a new central-nervous-system stimulant, was begun by Fabing[1] and others in February, 1953. Early in the course of study, the drug was used in the treatment of reactive depressions, narcolepsy, blepharospasm and spasmodic torticollis, and in these disorders it was shown to be more effective therapeutically than the amphetamines. In a group of over 100 patients with reactive depression, results of treatment were impressive. The side effects of the amphetamines, such as diminution in appetite and disturbances of nocturnal sleep, occurred not at all or rarely after administration of pipradrol. There was no change in the blood pressure, pulse rate, respiratory rate or pupillary size during the period of treatment. Fabing noted that the response of patients with reactive depression was sudden and dramatic, with elevation of mood and a quickening of retarded psychomotor state within two hours of administration of the first dose.

Patients with anxiety reactions without the depressive element, however, experienced exaggeration of their symptoms. In severe psychotic depressions, the drug was apparently inadequate, and electroconvulsive treatment was necessary. Results in other varieties of neuropsychiatric disorders have been less encouraging. The effects in ambulatory schizophrenia, pseudoneurotic schizophrenia, neurasthenia, presenile dementia, Huntington's chorea and arteriosclerotic psychoses were unimpressive. Similarly, the drug aggravated symptomatology in incapacitated obsessive-compulsive patients. The depressed phase accompanying parkinsonism is improved, as is the drowsiness brought about by routine medication in epilepsy.

Schut and Himwich[2] concluded that pipradrol is a central-nervous-system stimulant useful in the field of institutional psychiatry but with certain indications and contraindications. Pomeranze[3] made the following observation:

> . . . . a better attitude appeared to permit the obese subject to maintain dietary control and lose weight. The depressed subject displayed an increased alertness and a better interest in routine activities. This was quickly apparent and was well maintained throughout the day without any apparent interference with sleep. An additional advantage was that no tolerance developed.

Levy[4] used the drug in the treatment of depressive reactions diagnosed as part of a routine office examination in private practice. Antos[5] added pipradrol to chlorpromazine therapy to negate the drowsiness produced by that drug. He noted that all subjects experienced a "lift" during the day, without interference with sleep, and that the exhilaration commonly associated with amphetamine in the usual dosage did not develop.

Because of these reports, it was decided that pipradrol§ should be evaluated in certain specific reactive-depression states in the gynecologic field and as an adjunct to chlorpromazine therapy in the nausea and vomiting of early pregnancy. The results of such studies form the basis of this report.

PHARMACOLOGY

Pipradrol is a stimulant of the central nervous system, invoking its action in the subcortical area of the brain, specifically the reticular substance of the upper-brain-stem tegmentum. The cortex is in turn stimulated by this area. The drug is not sympathomimetic and does not evoke the undesirable findings associated with sympathetic stimulation such as hypertension, tachycardia, dilated pupils and sweating. Changes in the septal area of the brain of monkeys after intravenous administration were demonstrated by Heath.[6] Such a locus of action is said to be unique since this area is concerned with expedition of intellectual activity, which has cortical origin.

The pharmacology, site of action and indications are compared with those of amphetamine and chlorpromazine in Table 1.

In the original experimental work of Brown and Werner,[7] pipradrol was found to be of extremely low toxicity. Convulsions did not occur unless lethal doses were given intravenously, and effective doses did not alter blood pressure, pulse or respiratory rate. The margin of safety — that is, the difference between effective and lethal doses — is large.

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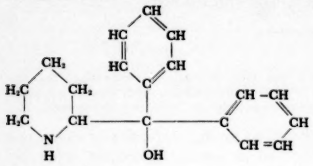
§Kindly supplied as Meratran by the Department of Medical Research, William S. Merrell Company, Cincinnati, Ohio.

Material

Eighty-one patients, ranging in age from nineteen to sixty-six years, were studied during the twelve-month interval, between May 1, 1954, and April 30, 1955. They were seen in the outpatient department and wards of the Free Hospital for Women and in our office. Thirty-four patients were given chlorpromazine for treatment of nausea and vomiting of pregnancy. Pipradrol was administered, adjunctively, to this group to lessen the drowsiness resulting from chlorpromazine therapy. The remaining 47 patients were treated with pipradrol alone. Eighteen of these patients suffered depression associated with the menopausal syndrome; 15 complained of premenstrual depression, 12 of postoperative depression, and 2 of post-partum depression.

Table 1. *Pharmacology, Action and Indications of Pipradrol, Amphetamine and Chlorpromazine.*



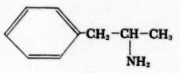
Pipradrol

Site of Action

Subcortical area & septal region

Indications

Emotional fatigue & depression



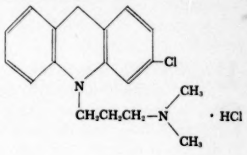
Amphetamine

Site of Action

Higher brain & upper spinal-column centers

Indications

Depression, fatigue, obesity, epilepsy & narcolepsy



Chlorpromazine

Site of Action

Cortical & subcortical levels in cerebrum & at diencephalon in medulla

Indications

Nausea & vomiting; agitated & disturbed patients; severe anxiety.

Table 2. *Results of Combined Therapy with Chlorpromazine and Pipradrol.*

Diagnosis	Total Cases	Marked Improvement	Moderate Improvement	No Improvement
		no. of cases	no. of cases	no. of cases
Nausea & vomiting of pregnancy	34	21	8	5
Postoperative depression	12	9	2	1
Post-partum psychosis	2	2	—	—
Menopause	18	12	2	4
Premenstrual depression	15	9	3	3
Totals	81	53	15	13

Results

Nausea and Vomiting of Pregnancy

We have observed good results with the oral administration of chlorpromazine for this complaint. A dose of 1 or 2 of the 10-mg. tablets did not seem to be effective; however, when the dose was increased to 25 mg., antiemetic activity was adequate in most cases although this dose produced almost constant lethargy and drowsiness. Thirty-four patients in the first trimester of pregnancy were given a 25-mg. tablet of chlorpromazine together with a 1-mg. tablet of pipradrol on arising, and this combination was repeated once or twice during the day as nausea appeared. In several cases 2 mg. of pipradrol was given with each dose of chlorpromazine. The results of this combination therapy are presented in Table 2.

Twenty-one patients noted marked improvement in nausea without associated central-nervous-system depression. The antiemetic effect of chlorpromazine did not seem to be affected by the newer compound. Eight patients were moderately improved — that is, they complained of slight intermittent nausea and still stated that they were somewhat drowsy while receiving the drug. Five patients were unimproved. They did not receive adequate emetic protection; moreover, they were overly excited, anxious and tense while taking the tablets.

Postoperative Depression

Twelve cases of postoperative depression were treated with 1 mg. or 2 mg. of pipradrol three times daily, usually beginning on the third postoperative

day. Nine patients were treated after total hysterectomy and bilateral salpingo-oöphorectomy, 2 after radical mastectomy, and 1 after a partial pelvic evisceration for cancer of the vagina. The patients subjected to hysterectomy were mostly thirty-five to forty-five years of age, the surgery being performed for benign conditions, usually endometriosis. They were treated because of the development of a profound depression, beginning usually on the third and occasionally on the fourth day after operation. Nine of the 12 patients were greatly improved with increased activity, ambulation, conversation with other patients and, in general, a better attitude toward convalescence. The following cases serve to illustrate the effect on 2 patients who became acutely depressed after radical mastectomy for carcinoma of the breast. Each patient, although aware of the possibility of cancer, had not really entertained that diagnosis and was stunned when told what had been accomplished.

Mrs. M.S. (F.H.W. 59442), a 45-year-old woman, was seen on February 11, 1955, because of a 2-cm. mass in the right breast that was freely mobile and not attached to the skin. One week later a frozen section demonstrated carcinoma, and a radical mastectomy was performed. On the 2d day, she was noticeably depressed, with episodes of crying, staring and immobility. Pipradrol therapy (1 mg. 3 times daily) was begun on the 3d postoperative day, and within 36 hours, her mood changed remarkably: she was up, had her meals on the sunporch and chatted with other patients. Therapy was continued for 1 month and was then suddenly interrupted, without recurrence of symptoms.

Mrs. J. G. (F.H.W. 60292), a 42-year-old woman, was seen on March 11, 1955, with a chief complaint of a lump in the left breast of 3 months' duration. She had noted nipple bleeding for 6 months. Resection of the left breast was done, and frozen section demonstrated adenocarcinoma; a left-sided radical mastectomy was performed on March 25. On the 2d day the patient did not reply to questions or was monosyllabic if she spoke at all. The nurses stated that she cried at frequent intervals and was worse when her family visited. Pipradrol, 1 mg. 3 times daily, was begun, and within 24 hours a pronounced elevation in mood occurred. After 48 hours, she was jovial and co-operative with the nurses, walked through the corridors and had pleasant visits with relatives. The drug was continued for 2 weeks, after which the dose was gradually diminished.

Nine of the 12 patients treated postoperatively were definitely improved; 2 noted moderate amelioration of depression, and 1 was unimproved (actually, this patient was a very tense, nervous woman with many basic conflicts regarding divorce, home life and income, and although she was in a depressed phase when treated, the patient selection here was poor).

Post-Partum Psychoses

Two patients were treated for typical post-partum psychoses developing two and three weeks after discharge from the hospital. In each case the basic personality pattern was immature, and the patient was unable to cope with added responsibility. Psychiatric consultation was obtained in both cases, and treatment with pipradrol instituted. The dose employed was 2 mg. three times daily. In both cases the immediate results were favorable. Neither patient has been followed for more than six months after delivery, but until the present time there has been no recurrence of the depressed state.

Menopausal Depression

Eighteen patients whose chief complaints were tiredness, weakness and lassitude occurring at the time of the menopause were treated with pipradrol. These women apparently were well stabilized so far as their vasomotor situation was concerned, since hot flushes and sweats were not bothersome. Their menstrual periods were usually diminishing in amount, with skips and delays. None were anemic, nor was any generalized metabolic disorder detected. Twelve patients described a gradual restoration of interest in everyday activities, increased alertness and ability to cope better with the trying situations of their age groups. Two patients noted some improvement, and 4 were unimproved or actually became worse after treatment. The dose employed in these cases was 1 mg. or 2 mg. three times a day.

It has been our custom to keep estrogens to a minimum in the treatment of the menopausal state as long as the uterus and cervix are "in situ." If possible, we prefer to explain the symptoms and irregularities of this changing period to the patient and attempt to get along without medication, or at most a barbiturate if she is tense or seems hyperreactive to her situation. We have preferred not to bring about vaginal bleeding of any degree in this age group because of the possibility of masking malignant conditions. Therefore, estrogens, if used at all, are given in small amounts and for short periods, and only for complaints of severe sweats and hot flushes. Pipradrol has seemed effective in combating many of the adjunctive symptoms of the menopausal state previously treated by estrogen or estrogen-androgen combinations.

Premenstrual Depression

This syndrome is probably etiologically related to the much publicized premenstrual tension. It is characterized by the development of lethargy, headache, disinterest and water retention, and occurs four or five days before the onset of the menstrual flow. Smith[8] has suggested absorption of endometrial catabolites with extracellular accumulation of sodium as a possible cause. Whereas certain subjects respond in a hyperirritable fashion, with excessive overt activity, temper tantrums and insomnia, others seem to enter a depressed phase. The latter group, it was thought, might respond well to pipradrol.

Fifteen women who presented such complaints were given 1 mg. three times daily, therapy beginning one week before the onset of menstruation. Nine noted appreciable improvement, 3 described some increased interest during the period of treatment, and 3 were unchanged. It is interesting that the 3 patients who were unaffected by pipradrol were also

not helped by amphetamines, salt restriction or diuretics.

Discussion

Evaluation of treatment in such varied conditions as nausea and vomiting of pregnancy, premenstrual and menopausal depression, and post-partum psychoses is indeed difficult. The presenting symptoms in themselves are subject to emotional stimulation and day-to-day change. No solid objective end point is available for accurate determination of results. There are no deaths to tabulate, and no morbidity to calculate. Necessarily, therefore, conclusions might better be described as impressions.

It is recognized, and has recently been shown,[9] that placebo therapy will afford about the same percentage of improvement in nausea and vomiting of pregnancy as most of the specific medications in vogue today. King[9] administered methamphetamine to elevate mood and thus to combat "psychologic" emesis and meclizine, in an independent series, to depress "physiologic" emesis. With the former the "improvement" rate was 61.5 per cent; with the latter it was 83.2 per cent. Placebos produced an "improvement" rate of 75.6 per cent (Table 3). The "improvement" rate with a combination of chlorpromazine and pipradrol was 85.2 per cent. The percentage increase in improvement with the combination over placebos in a small series is not of statistical significance. However, the purpose of this study — to determine whether pipradrol would eliminate the depression brought about by chlorpromazine in nausea and vomiting of pregnancy — was successfully accomplished in 21 of 34 patients.

Table 3. *Comparative Improvement with Drugs and Placebo.**

Drug	No. of Cases	Improvement
		%
Methamphetamine	26	61.5
Meclizine	43	83.2
Placebo	41	75.6
Chlorpromazine & pipradrol	34	85.2

*Based on data of King.[9]

Analysis of the results in the treatment of the various depressed states, whether postoperative, menopausal, premenstrual or post partum, suggests that the newer compound is of definite value in properly selected cases. Improvement, noted in 32 of 47 treated patients (68 per cent), occurred rapidly and persisted during the period of therapy. Withdrawal, however, resulted in a recurrence of the depressed phase. It should be emphasized that poor patient selection will result in such treatment failures as we experienced. Furthermore, dosage should be varied to suit the needs of the patient and increased or decreased as the situation demands.

Pipradrol is not a panacea for menopausal symptoms. In numerous cases in which subjective nervousness, headaches and crying spells are prominent, a mild sedative may be all that is required. In situations in which vasomotor instability seems to be paramount, a small dose of estrogen for a few weeks or possibly months will frequently stabilize the patient. In specific cases characterized by lassitude, disinterest and fatigability, however, the drug, in adequate dosage, will produce dramatic and rapid improvement.

Summary and Conclusions

A series of 47 cases with mental depression observed in various gynecologic and obstetric conditions is presented. Twelve patients had postoperative depression, 2 had post-partum psychoses, 18 had depressions associated with the menopause, and 15 had premenstrual tension. Thirty-four additional patients with nausea and vomiting of pregnancy were treated. Specific therapy for the underlying cause is discussed. The associated depressions were treated by the administration of a new antidepressant, pipradrol, in a dosage of 3 mg. to 6 mg. daily. The results were striking in that 65.4 per cent of the patients experienced substantial improvement, and 18.5 per cent moderate improvement; 16.0 per cent had no improvement.

This new antidepressant compound, when given in the dosage indicated, is an effective therapeutic agent in the treatment of mental depressions commonly encountered in the practice of obstetrics and gynecology.

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PATHOPHYSIOLOGY AND TREATMENT OF ADRENAL CRISIS*

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THE treatment of adrenal crisis has become an increasingly important topic for surgeons and internists. This derives from the ever-widening use of adrenalectomy as a therapeutic procedure in a variety of conditions. The consequent availability of bilaterally adrenalectomized patients has permitted a study of adrenal crisis and an analysis of its pathophysiology. It is the purpose of this paper to analyze the separate aspects of this syndrome and, on the basis of theoretical considerations and our own experience, to suggest a rational plan of therapy.

For some years the term adrenal crisis has implied a specific clinical situation — namely, that associated with the critically ill patient with Addison's disease. Unfortunately, this concept conceals the significant fact that the clinical situation is a synthesis of two distinct syndromes: that of sodium loss and that due to a deficiency of adrenal hydrocortisone. Conceptually and therapeutically, it then becomes important to distinguish between sodium depletion, deficiency of 17-hydroxycorticosteroids and a combination of the two.

There is nothing new in these statements. Twenty years ago the pre-eminence of sodium loss in the genesis of adrenal crisis was championed against the importance of the less well understood action of the steroids that enabled the organism to withstand stress. During this era Swingle and his co-workers,[1,2] in a series of penetrating experiments using adrenalectomized dogs, left little doubt that adrenocortical extract could correct the signs and symptoms of adrenal crisis, with little or no change in sodium balance. These findings, however, were generally ignored, coming as they did during the time of relative enthusiasm about the use of salt and desoxycorticosterone acetate (DOCA). Even at this time, however, it was recognized[3] that patients could die in adrenal crisis§ while in sodium balance and with normal serum electrolytes.

With the courageous performance of bilateral adrenalectomy by Huggins and Scott[4] in 1945, it was soon realized that life cannot be maintained in the adrenalectomized human being with salt or DOCA alone. Only with the availability of cortisone could total adrenalectomy be successfully managed although Green et al.[5] reported a successful adrenalectomy with the use of large amounts of adrenocortical extract. It became important, then, to inquire into the different requirements for cortisone between adrenalectomized patients and those with Addison's disease. It is now possible to resolve this apparent conflict and, in so doing, to gain an understanding of adrenal crisis.

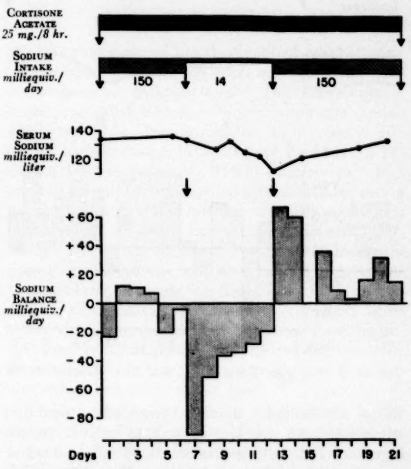

FIGURE 1. *Lack of Sodium Balance and Loss of Sodium in a Patient without Adrenal Glands.*

Three major points are discussed to provide a framework for consideration of these problems: *the adrenalectomized patient or the patient with Addison's disease) on maintenance doses of cortisone cannot conserve sodium on a low-sodium intake; the adrenalectomized patient cannot be maintained without a cortisonelike compound; and Addison's disease cannot be equated with bilateral adrenalectomy.*

Sodium after Adrenalectomy and in Addison's Disease

The absence of sodium conservation has been studied and confirmed many times in Addison's disease and after adrenalectomy.[6] Figure 1 represents a recent study of a patient without adrenal glands, receiving 75 mg. of cortisone and 14 milliequiv. of sodium daily. This patient had been moderately de-

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§For the purpose of this paper the term adrenal crisis is defined as the syndrome, described below, resulting from withdrawal of cortisone from the bilaterally adrenalectomized human patient.

pleted of salt at the time of study. Note the inability to come into sodium balance and the total loss of 273 milliequiv. of sodium (16 gm. of salt) in six days. At the end of this period, the patient was weak, anorectic, lethargic, subject to muscle cramps and hypotensive. She had lost weight; the blood volume was low, and the serum sodium had dropped.

This study parallels the usual course in the spontaneous development of the sodium-depletion syndrome in Addison's disease. The patient who has previously been maintaining sodium balance by the ingestion of 10 to 15 gm. of salt daily suffers a minor gastrointestinal upset, or excessive sweating. This leads to a decreased salt intake and the sequelae detailed above. If there are no other stressing situations, recovery may be obtained with salt, DOCA and supportive measures alone. It was this syndrome, previously termed adrenal crisis, that responded so well in the precortisone era to measures designed to restore the previously lost sodium. From a therapeutic, rather than a theoretical, point of view, it is now emphasized that this syndrome of severe salt depletion in adrenal insufficiency rarely occurs in a pure enough form to warrant administration of salt or DOCA alone.

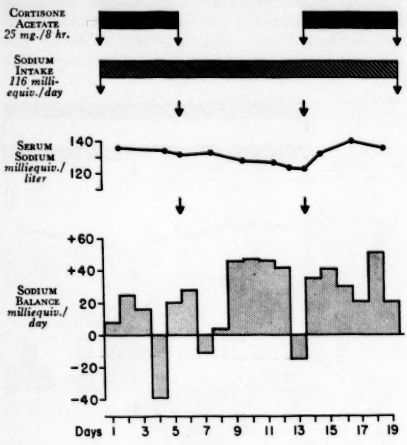

FIGURE 2. *Study of Sodium Balance after Adrenalectomy.*

Necessity of Cortisonelike Compounds

The fact that the adrenalectomized human being cannot be maintained without cortisone could not be appreciated until recently because of species difference. Ordinary laboratory animals, such as the rat and dog, could be maintained with salt or DOCA in reasonably good health, although the dog remains relatively fragile without cortisone. Recent work using the adrenalectomized monkey[7] confirms the necessity for cortisone in the primate.

Pearson et al.[8] have shown that salt-active hormones, such as DOCA, will not maintain life in the adrenalectomized human being, nor will aldosterone in physiologic doses.[6] Glycyrrhizin, which permits sodium conservation after adrenalectomy, is also inadequate to maintain life in human beings.[9]

The pure syndrome of cortisone deficiency can be seen in the adrenalectomized patient when the hormone is withdrawn and sodium balance maintained by daily sodium supplements, either by mouth or intravenously. The typical course of such a patient is as follows: after a day or two without cortisone, the patient becomes anorectic and listless and complains of stiffness or aching of the muscles, these symptoms being succeeded by weakness, lethargy, nausea and vomiting, fever, drop in blood pressure and postural hypotension; as the patient becomes severely ill, the systolic pressure reaches a level of 60 to 70 in the upright position and prostration ensues; this is usually accompanied by a high fever (temperature of 103 to 104°F.). When 100 mg. of hydrocortisone is given intravenously there is a rapid fall in temperature, a rise in blood pressure and a return of a sense of well-being within twelve hours. The course outlined can be compressed into thirty-six hours or may take ten days. The average time for the development of adrenal crisis is three or four days after withdrawal of cortisone given by mouth.

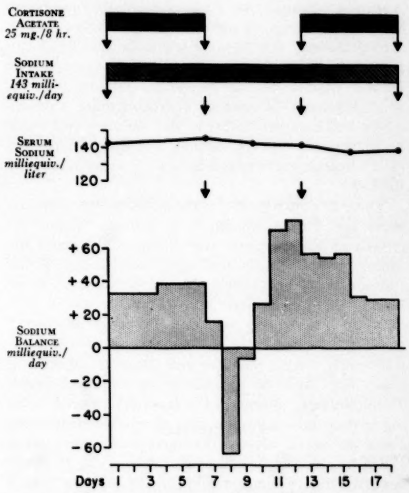

FIGURE 3. *Study of Sodium Balance in Another Adrenalectomized Patient.*

Figures 2 and 3 present sodium-balance studies on adrenalectomized patients from whom cortisone had been withdrawn. In each case, during the period of cortisone withdrawal, the sodium intakes were maintained by oral supplements or intravenous administration of saline solution. The period of cortisone withdrawal was terminated in each case by developing adrenal crisis.

To be noted are the positive sodium balances during cortisone withdrawal — the normal serum sodium in 1 and the decreased serum sodium in the other. The clinical picture was quickly reversed by cortisone, and the lowered serum sodium also returned to normal.

It is not the purpose of this paper to discuss the complex shifts of fluid and electrolytes in adrenal crisis. These have recently been considered in several publications,[10,11] and areas of disagreement are apparent. The significant point for this discussion is the development of adrenal crisis without external loss of sodium. The serum sodium remained normal or decreased, but any change noted could *not* be attributed to loss of sodium in the urine. Retention of water[11] and intercompartmental electrolyte shifts[10] may be involved in the changes that occur.

Addison's Disease and Bilateral Adrenalectomy

It has long been evident from carefully studied series of autopsies on patients with Addison's disease,[12-15] that the adrenal gland is seldom completely destroyed. In these series the glands are usually described as showing nests of cells beneath the capsule, or cortical adenomas. Clinically, it has been apparent that the disease is indeed a spectrum of varying degrees of adrenocortical insufficiency. Reforzo-Membrives, Power and Kepler[16] noted that some patients with seemingly classic Addison's disease acted as though they had remaining adrenal tissue. Two recent studies[17,18] have demonstrated that some patients have normal levels of plasma 17-hydroxycorticosteroids but no response to exogenous ACTH, implying the presence of a maximally active remnant of adrenocortical tissue. One of the patients[17] demonstrated progressive lowering of the plasma 17-hydroxycorticosteroids as the disease progressed.

Other stages of adrenal insufficiency exist. Two of our patients survived for three and six weeks after adrenalectomy without cortisone and were in only mild ill health. This was attributed to the presence of accessory adrenal tissue, which is commonly noted at autopsy[19,20] when a special search is made.

Still another point in the spectrum of adrenocortical insufficiency was apparent in a patient with Cushing's syndrome who was subjected to subtotal adrenalectomy. This patient remains in good health without cortisone, although we were unable to demonstrate any rise in urinary corticoids after prolonged stimulation with intravenously administered ACTH. An attempt has recently been made[21] to quantitate adrenal insufficiency after subtotal adrenalectomy.

These considerations lead to the conclusion that adrenal insufficiency varies gradually from the normal to that seen with bilateral adrenalectomy. Only when the adrenal gland is completely destroyed does the absolute dependence upon the 17-hydroxycorticosteroids become manifest. The analysis of Thorn and his associates[22] of a large series of patients with Addison's disease who were treated with salt and DOCA revealed varying degrees of rehabilitation with careful management. It is possible that the patients who were completely rehabilitated were those with the largest remnant of adrenal tissue.

Discussion

The cornerstone of the treatment of adrenal crisis with or without sodium depletion is adequate amounts of cortisone or hydrocortisone. The assumption is never warranted that the clinical syndrome is due solely to salt loss. We usually give an infusion of 100 mg. of hydrocortisone in 500 ml. of fluid over a period of four to six hours. It has been shown[23] that the half life of injected hydrocortisone is three and a half hours, or that this infusion rate will maintain a high level of circulating hormone with the effect persisting. During the period of intravenous administration of hydrocortisone, cortisone acetate is given intramuscularly, 50 mg. every four hours. This creates a depot of cortisone that will provide a supply when the need for intravenous infusion of fluids and hydrocortisone is diminishing. As the patient clinically improves, the cortisone is given orally and is gradually reduced to maintenance levels.

The intravenous use of fluids is best guided by the history of the illness and the clinical appraisal of the patient. In patients with spontaneously developing Addisonian crisis, a history of a prolonged period of anorexia and vomiting, weight loss and evidence of dehydration strongly suggests sodium depletion. Accordingly, the first intravenous administration should be 1000 ml. of 5 per cent glucose in saline solution, with 200 mg. of hydrocortisone added. It may be necessary to give a subsequent 1000 ml. of saline solution to a total of 300 milliequiv. of sodium. It is not necessary to replace immediately all the calculated or suspected sodium deficit. After this replacement, adequate cortisone dosage will later permit complete restoration of total body sodium.

In the opposite situation, that of an abrupt onset of adrenal crisis in either the patient with Addison's disease or the patient, adrenalectomized as a result of stress, such as infection or trauma, the fluid problem is quite different. In these cases there may be an excess of body water[11] or, as noted by McCullagh and Ryan,[24] an excess of body sodium in a patient receiving DOCA. The rapid infusion of large amounts of saline solution in such cases may precipitate pul-

monary edema. Such situations were seen by some of us before cortisone was readily available and have been sporadically noted throughout the literature. Thus, the recommendation for fluid is 5 per cent glucose in water with 100 mg. of hydrocortisone per 500 ml. This should be infused at an initial rate of 100 ml. per hour. Rates of infusion and concentration of hydrocortisone may have to be varied if hypotension and oliguria persist.

Occasionally, vasopressor drugs, such as levarterenol bitartrate (Levophed) and methoxamine hydrochloride (Vasoxyl), may be needed if hypotension is initially severe. Plasma and whole blood are not necessary. Since infection is a common precipitating factor in the genesis of adrenal crisis, antibiotics are strongly suggested. DOCA is unnecessary because, with the recommended high doses of cortisone, there is effective sodium retention.

There is no conclusive evidence that adrenocortical extract is as effective as hydrocortisone or that any unknown steroids in the extract have other important uses in the therapy of adrenal crisis.

It should be recognized, of course, that intermediate situations exist when there is some loss of salt as well as a severe lack of hydrocortisone. The serum sodium in these cases will not serve as an estimate of sodium depletion. Unless there is a reasonable assumption of excessive loss of salt, the initial solution should be 100 mg. of hydrocortisone in 500 ml. of 5 per cent glucose in water, for mild degrees of sodium depletion are well tolerated if sufficient hydrocortisone is given.

Summary and Conclusions

It is possible to separate the roles of sodium depletion and lack of 17-hydroxycorticosteroids in the genesis of adrenal crisis. It is proposed to reserve the term adrenal crisis for the syndrome developing because of a deficiency of these steroids. When sodium depletion is superimposed, this should be recognized and so stated. The point is stressed that administration of large amounts of hydrocortisone is of paramount importance in the treatment of adrenal crisis. Intravenous infusion of saline solution should be used only when circumstances suggest previous salt loss.

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MEDICAL PROGRESS

USE OF CHLORPROMAZINE AND RESERPINE IN MENTAL DISORDERS*

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WAVERLEY AND BOSTON, MASSACHUSETTS

THE last three or four decades have seen great progress in the treatment of mental disease by physical means. Syphilis of the brain and pellagra, both of which were formerly responsible for many admissions to mental hospitals, are no longer serious problems in America, owing to the development of specific cures for them. Insulin and electroshock have been useful in the treatment of manic-depressive and, to a lesser extent, schizophrenic psychoses. Hormones also have been helpful in patients with depressions[1] or with post-partum psychoses.[2]

A few years ago two chemical agents, chlorpromazine and reserpine, were introduced; they have already changed the practice of psychiatry. These drugs are currently called "tranquilizing agents" and will probably continue to be so designated, even though their action is not the induction of the state of serene security that the word "tranquility" connotes. It would more accurately describe their action to call them "deturmoilizers" or perhaps "apatheticatory agents." Irrespective of what they are called, however, there is no doubt of their beneficial action.

The effects of these drugs in man cannot be accurately evaluated, for several reasons. In the first place, there are no specific laboratory findings in schizophrenic or manic-depressive psychoses. All abnormalities thus far observed in these conditions — and there are many — are found in other diseases as well.[3] However, these nonspecific physiologic evidences of illness are helpful in assessing the effects of the treatment of mental disease.

Another fundamental difficulty in evaluating these effects is that the origin — and even the symptoms — of mental disease cannot yet be satisfactorily explained on a physiologic basis (or on any other basis). Fragmentary evidence pertaining to the mechanism of anxiety is available; these data have been reviewed elsewhere[4] and need not be detailed here. All that can be said with any confidence about the mechanism of anxiety is that it can be produced by intravenous infusions of epinephrine in doses too small to cause circulatory changes and that it can be produced by electric stimulation of the temporal lobe. Stimulation of this general area may also be followed by mood changes. The abnormal general awareness of internal and external stimuli exhibited by patients with mental disorders is probably related to changes in the function of the ascending reticular activating system, whose functions were defined by Magoun.[5] The mechanisms of the hallucinations described by such patients are not well understood; schizophrenic hallucinations are different in character and content from those that occur in normal subjects who have received hallucinogenic drugs. The mechanisms of delusions and of the loss of the ability to think abstractly — symptoms of the more serious mental disorders — are complete mysteries (as are the mechanisms of normal thought). It is evident, therefore, that no evaluation of the "tranquilizing" drugs can be based on their effects on the physiologic mechanisms of mental disease.

It is known that these drugs counteract in animals the electrophysiologic effects of various hallucinogenic agents, such as adrenochrome, lysergic acid and bufotenin. However, this fact is irrelevant to the present discussion; these substances do produce hallucinations in man, but it is not valid to regard schizophrenia as due to the presence in the body of some such substance. Not only are these hallucinations different from those of schizophrenia but also they are accompanied by electroencephalographic changes, which are uncommon in schizophrenia. Moreover, the normal subjects who have these induced hallucinations are able to discuss them calmly and objectively while experiencing them, unlike patients with mental disease, to whom their spontaneous hallucinations are real experiences. In addition, giving these agents to patients with schizophrenia does not aggravate the symptoms that they have at the time: the symptoms are changed or disappear, or new ones appear, but the specific clinical pictures exhibited are not made worse. The study of these hallucinogenic agents will undoubtedly increase knowledge of normal and abnormal neurophysiology, but it will probably not reveal much about the origin of schizophrenia.

Unfortunately, the favorable effects of the tranquilizing drugs can be described only in terms of behavior, and this circumstance makes objectivity difficult, since it involves value judgments. A semblance of objectivity is imparted to clinical evaluations of mental disease by the use of rating scales that employ numbers; nevertheless, these ratings are still based on personal judgments and cannot ever be objective. Value judgments depend largely on cultural bias — for example, some rating scales desig-

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nate increased sociability and conformity as indicative of improvement, whereas these changes might be taken as evidence of mental disease in some parts of New England.

Moreover, the clinical evaluations must be made by the attendant psychiatrists. Under these circumstances other sources of error inevitably arise: the psychiatrists did not know the patients before the illness began, and consequently they can never define the degree of return toward normal; psychiatrists who have spent many years working with the discouraging problems of chronic psychosis are likely to overrate small improvements; many state hospitals are in isolated communities, and since the staff members spend most of their time with the patients, they may gradually develop a somewhat distorted view of what is normal; and some psychiatrists are so much under the influence of some specific dogma as to become poor judges of behavior — statements and actions by patients that some physicians might regard as evidence of serious mental disease might be considered evidence of insight (and, therefore, of improvement in the patient) by some psychiatrists.

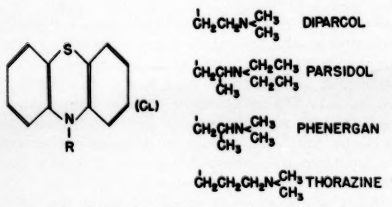

FIGURE 1. *Chemical Relations of Chlorpromazine.*

In particular, cultural phenomena influence the discharge rate of patients from mental hospitals: the tolerance of the community to which they return is a controlling factor. Some of the most favorable published reports on the effects of chlorpromazine and reserpine originated in parts of the country where community tolerance is high, or perhaps where the difference between people inside and outside mental hospitals is smaller than elsewhere.

A final difficulty in clinical evaluation of therapeutic measures in psychiatry deserves some comment: it is probably impossible for one mind to characterize another mind satisfactorily, since it is impossible for any operation to describe an operation similar to itself. Accordingly, psychiatric evaluations based on judgments of thinking and behavior must always be inadequate.

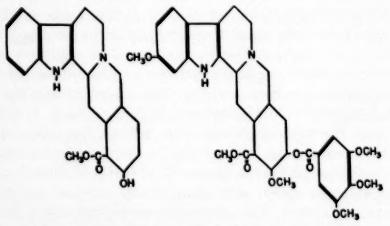

FIGURE 2. *Yohimbine and Reserpine.*

PHARMACOLOGIC CONSIDERATIONS

The chemical formula of chlorpromazine shows the relation of the drug to some others (Fig. 1). Diparcol and Parsidol are not much used in this country; the one is of some benefit in Parkinson's disease, and the other paralyzes the autonomic nervous system. Phenergan is a well known antihistaminic; the fact that it causes drowsiness has led some workers to conclude that much of its effectiveness in allergic states was due to its sedative action.

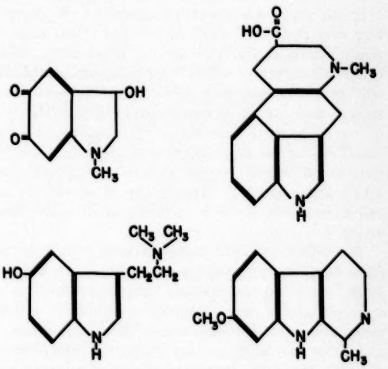

FIGURE 3. *Adrenochrome, Lysergic Acid, Bufotenin and Harmine.*

Reserpine (Fig. 2) is closely related to yohimbine, which in the past was reputed to be an aphrodisiac but is not much used at present. Reserpine contains an indole nucleus and is therefore related to the hallucinogenic drugs, adrenochrome, lysergic acid, bufotenin and harmine — and also, of course, to serotonin (Fig. 3).

The effects of chlorpromazine and reserpine on transmission or their action in counteracting the effects of hallucinogens on transmission through synapses in various parts of the animal brain will not be discussed here; such data are available but cannot yet be related to clinical phenomena.

Reported observations on neurophysiologic changes induced by the drugs are summarized in Table 1.

Some of these findings are not yet securely established, since they have not been corroborated. In addition, it is not clear what bearing the phenomena listed above have on the clinical changes induced by the drugs. Of particular interest regarding behavior, however, are the observations that chlorpromazine inhibits conditioned reflexes without greatly affecting avoidance responses whereas reserpine does not affect conditioned reflexes but does inhibit avoidance responses evoked by frightening stimuli.

TABLE 1. *Pharmacologic Data.*

TYPE OF ACTION	CHLORPROMAZINE	RESERPINE
Hypotensive effect	Rapid[6-8]	Slow[9]
Adrenolytic action	Moderate[6-8,10]	None[9,9]
Sympathetic-ganglion transmission	No effect[6-8]	No effect[11]
Hypothalamic reflexes	Depressed[8,12]	Depressed[11]
Vomiting	Markedly depressed[8]	Slightly depressed[13]
Activity of ascending reticular activating system	Depressed[14,15]	Enhanced[16]
Reflex reactivity of ascending reticular activating system	Depressed[10]	?
Sham rage	Depressed[17]	Depressed[18,19]
Conditioned reflexes	Depressed[20,21]	No effect (short of narcosis)[21]
Avoidance reactions	Slightly depressed[20,21]	Markedly depressed[9,20,21]
Reaction time (man)	No effect[22]	?
Finger-tapping speed (man)	Slowed[22]	?
Release of ACTH and responsiveness of adrenal cortex	No effect[9,23]	No effect[24]
Gastric secretion	Depressed[8]	Increased[9]

*Yohimbine, another Rauwolfia alkaloid, has some adrenolytic potency.

The action of chlorpromazine in depressing the reactivity of the ascending reticular activating system is also of interest in that it may explain the drug's effectiveness in allaying the hypersensibility that often occurs in neurosis.

CLINICAL EFFECTIVENESS

The drugs are highly effective in self-limited psychotic syndromes associated with hyperactivity and restlessness; these syndromes include manic disorders, schizoaffective states and some cases of early schizophrenia. The drugs are sometimes used in depressions accompanied by extreme agitation (for the control of the latter symptom), although it is recognized that they may exacerbate, or sometimes produce, depression. Chlorpromazine is probably the drug of choice in all such syndromes, since it usually works more quickly than reserpine; in fact, the latter often produces excitement before it quiets the patient. Chlorpromazine is usually given by intramuscular injection for a few days, after which oral medication is instituted. If chlorpromazine fails to quiet the patient, reserpine may be given in addition. The use of the drugs has greatly changed the treatment of these disorders. The patients eat and sleep well almost from the start, and their spontaneous recovery is thereby hastened; moreover, nurses and attendants are freed from the necessity of standing constant watch over excited patients (each of such patients formerly kept as many as three or four attendants fully occupied). In the absence of accurate data on the life histories of these syndromes, it cannot be stated how many of the patients greatly helped by the drugs would not have shown similar improvement with the older methods of treatment.

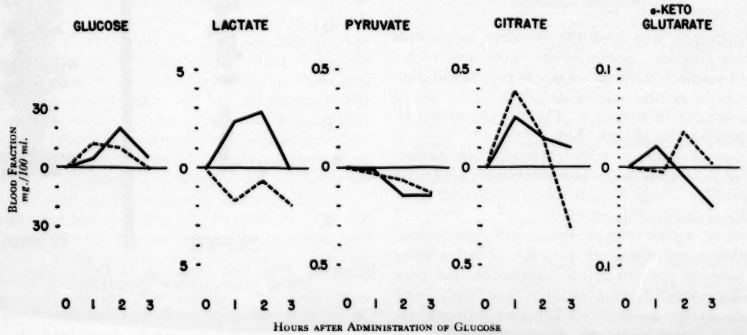

FIGURE 4. *Changes in Blood Carbohydrate Fractions in a Chronic Schizophrenic Patient after Oral Administration of 100 Gm. of Glucose.*

The solid lines indicate curves obtained before treatment; the broken lines indicate curves obtained while the patient was improved on reserpine. Only the curves for citric and alpha-ketoglutaric acid were abnormal before treatment, and they remained so.

Another acute syndrome that is greatly benefited by these drugs is delirium tremens, as are the closely similar syndromes that accompany withdrawal in drug addicts. Delirium tremens is a serious disease (15 to 55 per cent of patients who had it in a large municipal hospital died of it); the introduction of "tranquilizing" drugs has simplified the treatment

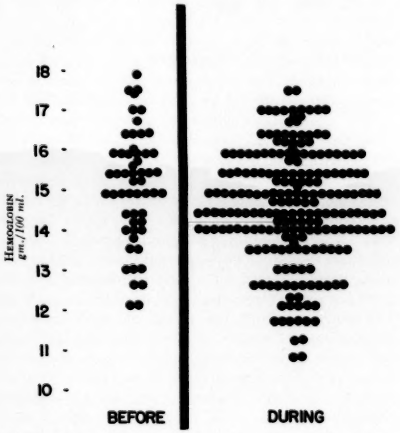

FIGURE 5. *Blood Hemoglobin Concentrations in 55 Patients before and during Treatment with Chlorpromazine. The apparent slight fall during treatment is specious, being due to relaxation of the venospasm commonly encountered in emotional disorders.*

and apparently improved the outcome in patients with this disorder. Similarly, the acute anxiety exhibited by addicts deprived of narcotic or barbiturate drugs can be greatly ameliorated through the use of chlorpromazine or reserpine. These drugs should be given parenterally in such cases.

Occasional patients with catatonia are greatly benefited — at least so far as the catatonic syndrome is concerned — when treated with reserpine; however, they remain schizophrenic.

Results of the use of chlorpromazine for the control of the symptoms of anxiety are difficult to evaluate; many neurotic patients are so suggestible that they report improvement, temporarily at least, after being given almost any medication. However, in most patients with severe recurrent anxiety or with some of its manifestations — including some types of headache and muscle spasms of the neck or back — the drug ameliorates these symptoms. Even more striking is the diminution of the hypersensibility — awareness of and hyper-reactivity to external and internal stimuli — that commonly accompanies neurosis. Most patients with these disorders report lasting benefit when given moderate doses by mouth.

The situation is different in the chronic psychoses. Patients with senile psychoses, with chronic schizophrenic or manic psychoses or with severe behavior disorders, in whom destructiveness, assaultiveness, aggressiveness and noisiness constitute therapeutic problems, often show improvement of these symptoms when given chlorpromazine or reserpine. One may be effective where the other is not, and it cannot be predicted which will work in any given case. These drugs have greatly improved the general status of patients with these syndromes: the use of electroshock treatments may be decreased by 75 per cent and that of lobotomies by 100 per cent, and the decline in destructiveness makes it possible to provide the patients with a more nearly normal environment.

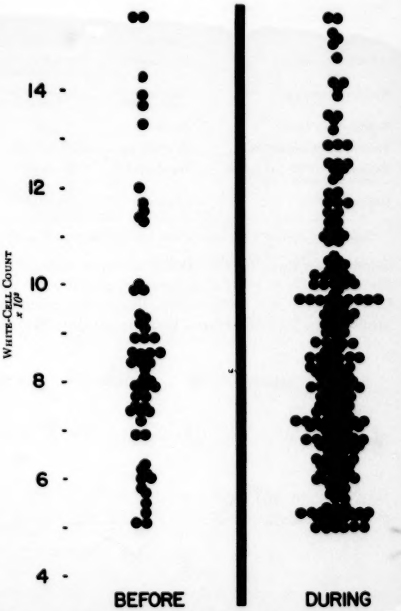

FIGURE 6. *White-Cell Counts in 55 Patients before and during Treatment with Chlorpromazine.*

On the other hand, probably no more than 15 or 20 per cent of these patients can be discharged; the delusions persist in all, as do hallucinations in most. The biochemical disorders that occur in chronically psychotic patients are not ameliorated, even when there is striking clinical improvement — in their behavior, that is, — not in their thinking (Fig. 4).

It is evident that chlorpromazine and reserpine change psychotic patients but do not cure them. In acute disorders the drugs create circumstances

that favor spontaneous remission; in chronic psychoses they greatly improve behavior, permitting discharge in a few cases and improvement of hospital environment in most of the others. These comments apply only to the findings reported in the literature so far. There is no way of knowing whether the use of the drugs over a period of years will benefit a majority of chronically psychotic patients enough to warrant their discharge.

At any rate, the changes in status of the patients will make it possible to answer a number of questions. Among these are the extent to which residence in the abnormal environment of the wards for chronically violent patients impairs the patients' chances of recovery and the validity of the claim (often made but never substantiated) that chronically psychotic patients would recover if their intractability did not prevent intensive psychotherapy.

Side Reactions and Their Absence

Chlorpromazine causes jaundice in about 1.5 per cent of patients who receive large doses by mouth; parenteral injection apparently does not have this effect. This suggests that during oral administration the drug either becomes excessively concentrated in the liver or is changed in some way by the alkaline pH of the intestinal juices. The jaundice usually disappears quickly when the drug is stopped; its course is apparently more prolonged in patients who are malnourished. Rashes also occur in some patients (often those with previous histories of allergies). In a series of over 200 patients no blood dyscrasias occurred — perhaps because no patient received more than 300 mg. a day (Fig. 5 and 6). Agranulocytosis has been reported in rare cases in patients who received large doses. Parkinsonism may also appear in patients given large doses; it wears off quickly when the drug is stopped. Weakness, dizziness and fatigue are often precipitated by the intramuscular use of chlorpromazine; these symptoms are probably of hypotensive origin. Drowsiness may occur when large doses are given by any route. Nasal congestion, dryness of the mouth and constipation are often experienced, but these are usually minor in degree.

Reserpine has no effect on the skin, the liver or the blood. It too produces weakness, dizziness and fatigue. Nausea, vomiting and diarrhea are common; Parkinsonism, nasal congestion and dryness of the mouth also occur. In addition, the drug often causes nightmares and erotic behavior; when given in large doses it usually causes transitory excitement in the second week of treatment. Increased gastric secretion and, occasionally, perforation of gastric ulcers have been reported to occur when large doses are given. (Chlorpromazine decreases gastric secretion.)

Except for the jaundice caused by chlorpromazine and the gastric perforations caused by reserpine, none of the complications of their use are very important. In fact, the absence of serious complications is noteworthy. Of particular interest is the ability of patients to take enormous doses of reserpine and large doses of chlorpromazine with little or no lasting hypotensive effect. This is probably due to the abnormal vasoconstrictor activity of their autonomic nervous systems.[25]

Chlorpromazine and reserpine have changed psychiatric treatment greatly in the last two or three years; as far as can be judged at present, their chief value in therapy is that they produce conditions favorable to recovery in acute, self-limited psychoses, ameliorate anxiety in many syndromes and make behavior, if not thinking, more nearly normal in chronic psychoses.

I am indebted to Roscoe B. Doughty, Ph.D., of the Science Information Department, Smith, Kline and French Laboratories, Philadelphia, for assistance in the preparation of this review.

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MEDICAL INTELLIGENCE

MULTIPLE CUTANEOUS CARCINOMA AFTER CREOSOTE EXPOSURE

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CREOSOTE is a fractionated chemical mixture obtained by the commercial distillation of gas or wood tars. The tar fractions distill over at various temperatures. Considering the upper limits of temperature in a still as an index, ammoniacal liquor and crude naphtha distill at 180°C., and light oil and carbolic (middle) oil at 225°C. Creosote oil distills at approximately 275°C., and anthracene oil and pitch distill at temperatures greater than 275°C. It is of interest that the three fractions with distilling points at 275°C. and higher — that is, creosote oil, anthracene oil and pitch — are carcinogenic.

Creosote is widely used in industry as a preservative for wood, lubricant for die molds, dip, fuel oil and in the manufacture of chemical preparations. Workers exposed to creosote are potential candidates for creosote dermatoses and carcinoma. This is particularly true of those in tar distilleries, carpenters, railroad workers, farmers, glass-furnace and steel-furnace attendants, and engineers and truckers of diesel fuel oil.

CASE REPORT

W. T., a 64-year-old man, was first seen on January 3, 1955, with a complaint of ulcers of the face. From 1947 to 1950, he worked in a shipyard painting creosote on planks and scows. The method of application was by hand brush, and no protective gloves were worn. Approximately 1 year after exposure his hands "broke out," and ulcerations developed on both cheeks and on the forehead. These remained stationary until 2 years before admission when they began to itch and bleed readily on slight trauma.

No other significant chemical exposure could be elicited. The patient has been a painter for 41 years and mixed his own paints, using lead and oils. Turpentine and white gasoline had been used as paint removers.

The past history was noncontributory. There was no history of previous skin disease or of any x-ray therapy.

A review of the systems was negative except for the skin and known cholelithiasis. There was no visual impairment.

Physical examination showed a well developed man presenting a superficial, ulcerated lesion, 3 by 3 cm., medial to the right supraorbital ridge, with similar ulcerations on both cheeks, the right measuring 1.0 by 1.2 cm. and the left 1.0 by 0.6 cm. In addition hyperpigmentation and hyperkeratotic papillomas were present on the face, neck and dorsum of both hands and fingers (Fig. 1 and 2). The remainder of the examination was within normal limits. The scrotal region was free of cutaneous lesions, and examination of the eyes revealed no abnormality. There was no significant palpable lymphadenopathy.

Routine examination of the blood and urine was negative, and x-ray films of the chest were normal.

On January 4 the forehead lesion was resected, and a full-thickness cervical dermal graft was applied to cover the defect. On February 8 both cheek lesions were excised, and the wounds closed by primary suture. Healing of all lesions was uneventful.

Microscopically, the lesions consisted of a proliferation of cells of the basal type invading the superficial portion of the corium in irregular, reticulated strands (Fig. 3). In the centers of some of the strands, the cells showed early to advanced keratinization, with occasional pearl formation. The peripheral cells were palisaded in the manner characteristic of basal-cell carcinoma. The principal point of interest was the marked inflammatory infiltrate, consisting for the most part of lymphocytes, plasma cells and an occasional cluster of polymorphonuclear leukocytes. This infiltrate was compact, filling the upper corium and completely surrounding the carcinoma. There was a small focus of erosion of the tumor, with collections of polymorphonuclear leukocytes in the center of the surface of the growth. The final diagnosis was mixed basal-cell and epidermoid carcinoma with marked inflammation.

FIGURE 1. *Macular and Papular Lesions, Showing Pigmentary Changes and Hyperkeratosis.*
The lesions were dry and scaly, ranging from pink to brown in color.

The patient returned for follow-up examination on October 14 with 2 new lesions of 2 months' duration. An elevated pearly lesion, 8 by 9 mm., was situated in the right preauricular region, and a superficial ulcer, 8 by 6 mm., just below the right inner canthus. There was no significant preauricular or cervical lymphadenopathy. Both lesions were completely resected. Microscopically, the ulcerated area was interpreted as basal-cell carcinoma, and the elevated lesion as mixed basal-cell and epidermal carcinoma.

DISCUSSION

The tumorigenic properties of creosote were first appreciated in 1898, when Mackenzie[1] reported a case of scrotal papillomatosis in a creosote worker. Subsequently, Cookson[2] recorded the carcinogenic activity of creosote in a sixty-six-year-old man who had worked for thirty-three years in a creosote factory. After eighteen years of exposure, a lesion was discovered on the dorsum of the right hand. Micro-

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scopical examination of this lesion, which ultimately fungated and was treated by circular amputation above the elbow, was interpreted as showing squamous epithelioma; the patient died two months later. Post-mortem examination revealed metastases to the lungs, liver, kidneys, heart and axillary lymph nodes.

Experimentally, Sall and Shear[3] have demonstrated the growth of epitheliomas in the skin of mice painted with creosote oil in benzene. Poel et al.[4] tested the distillates from by-product coke ovens by its application in benzene or toluene to the shaved interscapular areas of mice. They were able to produce malignant papillomas. They also bioassayed the crude-tar and pitch residuum after fractional distillation and found carcinogenic activity. Among the fractions tested and found to be actively carcinogenic were two grades of creosote oil and a "crystal-free anthracene oil" widely used as a wood preservative.

FIGURE 2. *Lesions of the Hand.*
The "warty," hyperkeratotic papillomas are multiple and irregular in size and shape. Pigmentary changes are present. (These lesions are regarded as precancerous.)

Although creosote carcinogenesis has been noted in the lung and eye, the primary site of predilection is the skin. The dermatoses that have followed prolonged contact with creosote are characterized by multiple lesions of macules, papules, keratosis, verrucae and varying degrees of telangiectasia and pigmentation. Spontaneous regression may occur but is not a notable feature. Malignant degeneration may also occur, and it is reasonable to assume that the longer the interval after exposure, the greater the malignant potential.

The feature of the latent period and the multiplicity of the lesions are characteristic of induced cutaneous neoplasia. The usual sites of occurrence of creosote carcinomas are the face, the forearms, the dorsum of the hand, the scrotum and the knees.

FIGURE 3. *Photomicrograph of a Typical Lesion, Showing Proliferation of Cells of the Basal Type Invading in Irregular, Reticulated Strands.*
Pearl formation is seen. The characteristic point of interest is the marked inflammatory infiltrate, consisting essentially of lymphocytes and plasma cells.

Histologically, the lesion is a squamous-cell carcinoma with basal-cell proliferation and carcinoma. Pearl formation and keratinization may be seen. Necrosis is not generally a feature, but a dense inflammatory area is characteristically seen surrounding the carcinoma. This inflammatory infiltrate usually consists of lymphocytes and plasma cells. Regional-lymph-node metastasis may occur but is not common. The prognosis is generally more favorable than that of spontaneous cutaneous squamous carcinoma.

SUMMARY

A case of 5 primary cutaneous carcinomas of the face after creosote exposure is presented. The oc-

cupational hazards, clinical features, histology and creosote carcinogenesis are discussed.

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I am indebted to Dr. Olive Gates, New England Deaconess Hospital, for the detailed pathology analysis and to Mr. Leo Goodman, Mallory Institute of Pathology, Boston City Hospital, for the excellent photographs.

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DIPHENYLHYDANTOIN SENSITIVITY*

Report of Fatal Case with Hepatitis and Exfoliative Dermatitis

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IT has been well recognized that untoward effects may follow the extended ingestion of diphenylhydantoin sodium (Dilantin) and may at times prove fatal.[1,2] Sensitivity to this agent has resulted in fatal disseminated periarteritis nodosa in 1 reported case,[3] and has been held responsible for inducing the "L.E." phenomenon.[4] The particular manifestations that resulted in the fatal outcome recorded below are not well recognized, and, consequently, a proper diagnosis was made only after delay and confusion.

Case Report

R.S., a 29-year-old Negro factory mechanic, was first hospitalized on March 1, 1953, because of lethargy after a convulsive seizure. There had been 5 previous convulsions over the past 15 months. Aside from confusion and a minimal blood-pressure elevation, the physical status was unremarkable. An investigation of the central nervous system, including a lumbar puncture and roentgenograms of the skull, was negative. An electroencephalogram was abnormal, demonstrating diffuse and slow activity in paroxysms, a finding regarded as consistent with a convulsive disorder. It was concluded that the patient suffered from idiopathic grand-mal epilepsy, and he was accordingly placed on diphenylhydantoin therapy, consisting of 0.1 gm. 3 times daily. He resumed normal activities and, when seen in the clinic 3 weeks later, was without complaints. He continued to be well until about the 2d week in April, when he noted the onset of a "pimply" rash on the forearms and hands. This rash cleared in about 3 days, but during the next week he felt below par, had discomfort in his throat and became febrile. His physician administered 300,000 units of penicillin and placed him on 4 gm. of 3, 4-dimethyl-5-sulfanilamido-isoxazole (Gantrisin) daily in divided doses. Despite these efforts the rash returned and rapidly became generalized and exfoliative. In addition it was noted that generalized lymphadenopathy and jaundice had developed. A provisional diagnosis of scarlet fever was made, and he was referred back to the hospital on April 27.

Physical examination revealed an acutely ill man with a temperature of 100.4°F. The scleras were deeply icteric. There was a generalized desquamating eruption most prominent over the face, scalp and upper trunk. Where intact, the skin had a diffuse erythematous flush. The tongue was diffusely reddened. The lymph nodes showed generalized enlargement and were firm and nontender. The liver edge extended 3 fingerbreadths below the right costal margin, and the organ was firm and tender. The spleen was not palpable. The circulating-white-cell count was 19,000, with 35 per cent eosinophils and 15 per cent abnormal lymphocytes. The urine contained albumin and was deeply bile stained. The blood chemical values at the time of admission and during the subsequent hospital course are listed in Table 1.

There was considerable discussion regarding the nature of the illness, confounded in part by the fact that its most prominent manifestations — namely, jaundice and exfoliation — were noted after the patient had been given penicillin and Gantrisin. Although the possibility of a generalized hypersensitivity phenomenon was considered and these drugs were withheld, the initial working diagnosis settled on was infectious mononucleosis. Treatment was withheld pending further observation and clarification of the problem, but unfortunately diphenylhydantoin was not discontinued until the 3d hospital day. The heterophil-antibody titer after guinea-pig absorption was negative, and by the 3d day it was apparent that further control observation would be of no advantage. Accordingly, cortisone treatment was begun on the 4th hospital day, with an initial daily dose of 400 mg. followed on the succeeding day by 300 mg. and then a maintenance dose of 200 mg. The patient's condition had grown progressively more grave in that the rash came to involve an ever-increasing area of skin with exfoliation, the temperature chart showed an intermittent septic-type curve, with early evening peaks of 103.1°F., and the serum chemical values implied progressive compromise of liver function associated with jaundice, azotemia and acidosis. Whereas the skin exfoliation seemed to decrease after 2 days of cortisone therapy, the general process had extended to include ulceration about the lips, eyes, oral cavity, anus and genitals, and the patient grew weaker and more lethargic. Because of the widespread injury to the natural barriers against infection, chlortetracy-

TABLE 1. *Blood Chemical Values.*

Hospital Day	Urea Nitrogen	Icteric Index	Carbon Dioxide	Chloride	Sodium	Potassium	Total Protein	Albumin-Globulin Ratio
	mg./100 ml.		*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*milliequiv./liter*	*gm./100 ml.*	
2	40	95	20	99			4.6	2.9:1.7
5	95*	150	15	92	120	6.9	6.7	4.7:2.0
7	117	160	19	94	128	5.2	6.0	3.2:2.8
9	116	192	24	110	150	4.7	6.5	3.2:3.3

*Nonprotein nitrogen, 203 mg. per 100 ml.

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cline prophylaxis was added to the treatment schedule. Because the ulceration of the oral cavity extended, it was necessary to give this medication parenterally.

After 3 days of cortisone administration, there was striking regression of the lymphadenopathy and eosinophilia, and the temperature remained at normal levels. Despite this, the patient gave no gross signs of rallying, and the serum chemical values indicated increasing jaundice and azotemia. The prothrombin deficiency failed to respond to the administration of vitamin K_1 oxide, and by the 8th hospital day he was actively bleeding into the ulcerated mucosal areas. His appearance at this time is shown in Figure 1.

In addition to the measures mentioned above, he was given 100 milliequivalents of potassium on the 8th hospital day and a 500-ml. blood transfusion on the 9th. The former measure was carried out because of changes in the serial electrocardiograms consistent with those seen in hypokalemia. The serum potassium values remained normal. He died on the 10th hospital day.

At autopsy, the most striking finding was a severe hepatitis, with widespread necrosis of the liver. Grossly, the liver weighed 1730 gm.; it was greenish brown and flabby in consistence but without obvious necrosis. On microscopical section, however, the usual lobular architecture was completely disrupted by widespread areas of necrosis of hepatic cells in which there were dilated sinusoids whose lining Kupffer cells contained brown pigment (Fig. 2). Bile plugs were seen filling many of the canaliculi and small

FIGURE 1. *Appearance of the Patient on the Eighth Hospital Day.*

bile ducts. In addition, there were acute necrotizing hemorrhagic bronchopneumonia, mild acute hemorrhagic pancreatitis and cholemic nephrosis. There were no findings suggestive of periarteritis nodosa.

DISCUSSION

As mentioned above, it was not appreciated initially that sensitivity to diphenylhydantoin could account for this picture. In 1950 Chaiken et al.[5] reported a case remarkably similar in all respects to that presented above, except that the patient did not die. In their case the manifestations were exacerbated by readministration of the drug, so that there can be no confusion about the etiologic agent. They noted that theirs was the first reported case of jaundice from this cause. Fortunately, the more common manifestations of sensitivity to this agent are less catastrophic than those reported above.

Although detailed discussion is not possible in this brief report, it is noteworthy that the serum protein

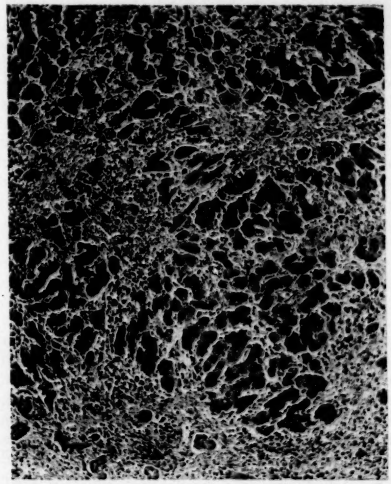

FIGURE 2. *Section of the Liver (Hematoxylin and Eosin Stain X625).*

levels and cephalin-cholesterol flocculation returned to normal values in the face of overwhelming and progressive liver destruction.

SUMMARY

A case of fatal hepatitis with jaundice, exfoliative dermatitis, eosinophilia and lymphadenopathy considered to be due to diphenylhydantoin (Dilantin) sensitivity is reported.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 42111

PRESENTATION OF CASE

First admission. A four-month-old female infant was admitted to the hospital because of cyanosis and convulsions.

At birth there was difficulty in initiating breathing, and oxygen was administered for four or five days. At home the baby sucked poorly but was otherwise asymptomatic until three weeks before admission, when it was noted that she flexed and extended her legs, screamed, rolled her eyes, became cyanotic and finally went limp, with gasping respirations. Similar spells recurred three or four times daily, usually after feedings.

The family history and pregnancy history were noncontributory.

Physical examination revealed a pale infant who became cyanotic on crying. The lungs were normal. The heart was of normal size. There was a Grade 3, harsh, systolic murmur heard over the entire precordium, loudest in the third left intercostal space near the sternum. The aortic second sound was greater than the pulmonic. The liver edge was palpable 2 cm. below the right costal margin. Peripheral pulses were palpable, and there was no clubbing.

The temperature was 99.4°F., the pulse 100 and regular, and the respirations 29. The blood pressure was 60 systolic (with blanching) in the arm, and 55 in the leg.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 10,800, with a normal differential. An electrocardiogram showed a sinus tachycardia at a rate of 140 (axis +100°) and upright T waves in Leads V_1 through V_6. X-ray examination of the chest revealed somewhat avascular lung fields and a concavity on the left border of the heart (Fig. 1). The apex was elevated slightly above the left leaf of the diaphragm. Skull films were normal.

The hospital course was uneventful, and the infant was discharged on the sixth hospital day.

Second admission (six months later). One month before admission the patient received penicillin for an upper respiratory infection. After this the spells increased to six or seven a day, were accompanied by rigidity of the extremities and hyperextension of the head, and were followed by a deep sleep for fifteen to twenty minutes.

Physical examination was unchanged except for the presence of slight cyanosis of the lips and nailbeds, and clubbing of the fingers. The temperature was 99.4°F., the pulse 156, and the respirations 40.

Urinalysis showed a + test for sugar and 10 to 12 white cells per high-power field in the sediment.

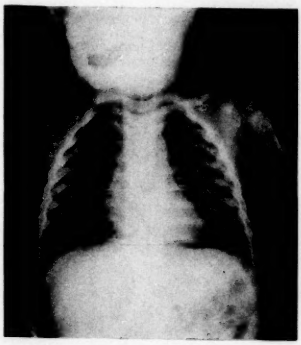

FIGURE 1. *Roentgenogram of the Chest.*

Examination of the blood revealed a hemoglobin of 16.0 gm. per 100 ml. and a white-cell count of 13,600, with a normal differential. An electrocardiogram showed right-axis deviation, but there was no definite evidence of right ventricular hypertrophy. An x-ray film of the chest was as before except that the lung fields appeared better vascularized. The patient had no "spells" in the hospital and was discharged on the sixth day.

Final admission (seven months later). Since discharge she had experienced three or four "spells" a day lasting ten to thirty minutes. Ten days before entry she was given penicillin for a "cold." Three hours before admission an attack was accompanied by continuous clonic movements of the arms, rigidity of the legs and hyperextension of the head. This did not improve with home administration of oxygen and tincture of opium.

On physical examination the patient was cyanotic and semistuporous, and had grunting respirations. There was slight injection of the throat, tonsils and left tympanic membrane. Physical examination was otherwise unchanged from before.

The temperature was 98°F., the pulse 92, and the

respirations 20 to 30. The blood pressure was 92 systolic, 70 diastolic.

Urinalysis was normal. Examination of the blood revealed a hemoglobin of 14.2 gm. per 100 ml., a hematocrit of 63 per cent and a white-cell count of 18,800, with 82 per cent neutrophils. A smear disclosed marked variation in the size of the red cells, with many macrocytes and a moderate number of microcytes. There was considerable polychromatophilia.

After oxygen and morphine the convulsions slowly subsided, and cyanosis decreased. However, prolonged attacks of cyanosis, with labored respirations and impaired consciousness, continued to occur. The temperature ranged for the most part between 97 and 100°F., although on one occasion it dropped to 94°F. The lungs remained clear to percussion and auscultation. Neurologic examination was negative except for the presence of a depressed state of consciousness. Lumbar puncture on the fourth day showed 2 lymphocytes per cubic millimeter, with a protein of 17 mg. and a sugar of 107 mg. per 100 ml. and a negative culture. An electroencephalogram was normal. A blood culture was negative. Throat culture showed abundant alpha-hemolytic streptococci, and urine culture, a few coliform organisms. On the eighth hospital day Crysticillin and streptomycin were begun. On the eleventh day opisthotonos and carpopedal spasm were noted during a cyanotic attack. A positive Chvostek sign could not be elicited, however. With morphine and calcium gluconate, respirations became normal, cyanosis diminished, and carpopedal spasm disappeared. On the next day the patient had several more attacks accompanied by opisthotonos and carpopedal spasm. She did not now respond to painful stimuli; there was ptosis of the right eyelid, and the right pupil was three times larger than the left. Funduscopic examination showed engorgement of the veins. On the thirteenth day, while the patient was in moderate carpopedal spasm the total protein was 5.4 gm., the calcium 8.0 mg., the potassium 2.8 mg., and the iron 56 microgm. per 100 ml.; the carbon dioxide was 23 milliequiv. per liter, and the pH 7.43. On the seventeenth day the white-cell count was 54,000, and the temperature began to spike, reaching 102 to 104°F. The breath sounds became bronchial. On lumbar puncture two days later the cerebrospinal fluid contained 3 lymphocytes per cubic millimeter and 69 mg. of protein and 110 mg. of sugar per 100 ml., and a culture was negative. On the twenty-first day the temperature began to level off to 96°F., with small spikes, and petechiae were noted on the face and neck. The patient died on the twenty-fifth hospital day.

Differential Diagnosis

Dr. Edward F. Bland:* There are two problems in this infant: the structural defects in the heart and the cause of death. After a difficult start at birth she was quite well until three weeks before admission, when alarming symptoms, which usually indicate a serious degree of cerebral anoxia, appeared. After the onset of such symptoms it is unusual for a child to live quite so long. The presence of cyanosis, clubbing and an elevated hematocrit is helpful, for they indicate a shunt between the right and the left side of the heart permitting venous blood to enter the systemic circulation. They rule out a number of serious conditions that may be seen in newborn infants such as idiopathic enlargement of the heart, abnormal origin of a coronary artery from the pulmonary artery and von Gierke's syndrome. I am left, then, with some combination of defects that will permit a child to live, be fairly well for the first few weeks and then deteriorate in a serious fashion. On the law of chances the most likely condition is the tetralogy of Fallot. There are a few features against it. In most patients with lesser degrees of the tetralogy, the life span is longer than this; they often survive the early years. You are all probably familiar with Dr. White's and Dr. Sprague's celebrated patient who lived to be sixty years of age.[1] That long a life, of course, is exceptional. The second bothersome point is the quibbling about the electrocardiogram, which showed right-axis deviation but which may or may not have shown right ventricular hypertrophy. The hypertrophy pattern is usually unequivocal in patients with the tetralogy of Fallot. With that in mind I shall ask Dr. St. Aubin to interpret the x-ray films. Were the lungs avascular? Was there an absence of or a marked diminution in the area of the pulmonary conus?

Dr. Paul M. G. St. Aubin: The films of the chest taken during the first admission (Fig. 1) demonstrate a normal bony thorax and diaphragm and avascular lung fields. The apex of the heart appears lifted off the left leaf of the diaphragm.

Dr. Bland: That means hypertrophy of the right ventricle, does it not?

Dr. St. Aubin: Yes. There is notching of the upper portion of the left border of the heart, a decrease in the size of the hilar vascular markings and a definite deficiency in the pulmonary vascular markings. One film was reported as showing relatively normal pulmonary vascular markings, but I do not agree with this interpretation. In children of this age the pulmonary vascular markings are somewhat prominent. The right anterior oblique projection taken after barium was swallowed, demonstrates an increase in the size of the cardiopulmonary window.

Dr. Bland: Does that mean a small pulmonary conus?

Dr. St. Aubin: It means a small pulmonary artery.

Dr. Bland: Is the aorta too far to the right, or is it in normal position? Is it narrowed?

Dr. St. Aubin: The arch and the descending por-

*Physician, Massachusetts General Hospital.

tion are remarkably well seen for a child of this age.

DR. BLAND: In summary, do you agree that there is hypertrophy of the right ventricle, a small conus, a small pulmonary artery and avascular lungs?

DR. ST. AUBIN: I do not see the conus; I see an enlarged right ventricle, a small pulmonary artery and deficient vascularity in the lungs.

DR. BLAND: The Grade 3, harsh, systolic murmur associated with cyanosis and clubbing also suggests the tetralogy of Fallot or some variant of it, and the findings in the x-ray films are entirely in accord with that diagnosis. The four aspects of the tetralogy are stenosis of the pulmonary artery or infundibulum, usually giving a diminished shadow in that area; a defect in the interventricular septum; an aorta that overrides both ventricles so that blood from both sides enters the systemic circuit, aided and abetted by the obstruction at the pulmonary orifice; and hypertrophy of the right ventricle. Incidentally, we usually find right ventricular hypertrophy demonstrated in the electrocardiogram and by avascular lung roots.

Why was this child so well for a few weeks? Sometimes, these infants are well for a few weeks because the ductus arteriosus remains open. Closure may be delayed for a few weeks up to a year or so. Seventeen months is unusually long. I suspect that this child was temporarily well because the ductus arteriosus did not close and permitted a fair amount of blood to go into the pulmonary circulation. Dr. Helen B. Taussig's astute clinical observation that infants with pulmonary stenosis in whom there was delayed closure of the ductus were less cyanotic than those in whom the ductus closed normally gave her the idea for the so-called Taussig–Blalock operation,[2] since a patent ductus was one way of compensating for pulmonary stenosis. Sometimes, patients with the tetralogy do not live for more than a few weeks because there is a high degree of pulmonary stenosis even to complete atresia of the orifice.

I can think of no diagnosis that covers the findings in this infant so well as some variant of the tetralogy of Fallot, with probably a high degree of pulmonary stenosis and a delayed closure of the ductus arteriosus.

The next problem is why the child died. Many infants ultimately succumb to infection, which may be bacterial endocarditis with emboli to the brain and even abscess formation in the brain. The terminal events in the infant under discussion suggest a focal lesion in the brain. I should be highly suspicious that this child had either an acute or subacute bacterial endocarditis. On the other hand, cyanotic children with severe infections and associated dehydration not uncommonly have thromboses, especially in the cerebral vessels, with resulting cerebral infarction. That is another possibility here, but because the course at the end was so rapidly downhill, I suspect that there was bacterial endocarditis, with cerebral complications.

In summary, I believe that this infant had either the tetralogy of Fallot or a variant of it, probably with a high degree of pulmonary stenosis and possibly with a delayed closure of the ductus arteriosus. The condition was complicated by either bacterial endocarditis with cerebral emboli and abscesses or cerebral thrombosis with infarction.

DR. JOHN MACK: One point that was not mentioned in the protocol was that blood was seen coming from the patient's mouth during the last admission.

DR. ROBERT E. SCULLY: From the record, which mentioned blood in the mouth on one occasion, I got the impression that the bleeding was attributed to mucosal erosion by the feeding tube.

DR. MACK: Crusted blood was seen on several occasions, and we were not satisfied that the tube was the explanation for it.

DR. BLAND: Do you have any films taken on the last admission, Dr. St. Aubin?

DR. ST. AUBIN: Yes; they show very little change from the previous studies. The configuration of the heart is more normal; the lungs are still avascular.

DR. BLAND: Can you identify pulmonary infarcts?

DR. ST. AUBIN: There is no evidence of consolidation or atelectasis in the lungs suggesting infarcts.

DR. SCULLY: Dr. Friedlich, you saw this patient; have you a comment?

DR. ALLAN M. FRIEDLICH: We were fascinated by the possibility of hemoptysis to explain the bleeding. This more frequently occurs in patients with cyanotic congenital heart disease who have marked pulmonary hypertension. This patient did not appear to have that problem. We have seen hemoptysis in 1 other patient with a tetralogy of Fallot. There are many aspects of the treatment and management of this patient that might be discussed. Why was the operation not carried out sooner in an infant with desperate symptoms — namely, the peculiar paroxysmal attacks of cyanosis and dyspnea, with loss of consciousness? If these attacks can be controlled, it is easier and less risky to operate when the child has grown some. Moreover, if a shunt operation is done at this early an age, the growth of the child often makes reoperation necessary at a later age. However, if the spells become very severe and frequent, one's hands are sometimes forced. I think that was one of the reasons that this child was admitted the last time.

DR. LAWRENCE H. WARBASSE, JR.: What do you think the explanation of the periodic spells was?

DR. BLAND: I suppose they were caused by cerebral anoxia. We see them occasionally in infants who do not have the cyanotic type of heart disease but who probably have circulatory failure or low blood pressure. We have seen them in children with von Gierke's disease. We saw them also in the celebrated case[3] of the infant in whom the left coronary artery arose from the pulmonary artery; that child

had attacks after nursing, and became very agitated, pale and obviously distressed. We decided in retrospect that he had angina pectoris. Finally, he lost consciousness and slept for ten or fifteen minutes so that the attack was comparable to a convulsion.

Clinical Diagnoses

Tetralogy of Fallot.
?Cerebral abscess formation.
?Bacterial endocarditis.
?Cerebral thrombosis and infarction.

Dr. Edward F. Bland's Diagnoses

Tetralogy of Fallot, with probable marked pulmonary stenosis.
?Patent ductus arteriosus.
?Bacterial endocarditis, with cerebral embolism and abscess formation.
?Cerebral thrombosis, with infarction.

Anatomical Diagnoses

Tetralogy of Fallot.
Endocarditis, nonbacterial, thrombotic, subpulmonary tract, recent.
Thrombosis, right atrium, recent.
Pulmonary emboli and infarcts, recent.
Cerebral emboli and infarcts, recent.
Thrombosis of dural sinuses and cerebral veins, recent.
Systemic and pulmonary fat embolism, slight.

Pathological Discussion

Dr. Scully: At autopsy this infant had more extensive disease than one might expect from the clinical abstract. The heart showed the essential features of the tetralogy of Fallot. The wall of the right ventricle was greatly hypertrophied, measuring 6 mm. in thickness. The pulmonary artery was somewhat small. The pulmonary valve was normal. However, below the valve, there was marked stenosis (Fig. 2). The narrowing was chiefly muscular, but was partially a result of endocardial thickening. On the endocardial surface of the subpulmonary tract, there were several large, warty, friable vegetations (Fig. 2), which we thought at the time of gross examination were bacterial. This excited us because bacterial endocarditis is unusual in the tetralogy at this age.[4] Later, we discovered that our interpretation of the vegetations was incorrect. The aorta was dextroposed and overrode an interventricular septal defect, completing the picture of the tetralogy. The foramen ovale was patent to a probe. The ductus arteriosus was open, but its lumen at the time of death was of small caliber. In addition to the thrombi below the pulmonary valve, there was a fresh thrombus in the right atrial appendage. The lungs had undergone massive embolism and infarction involving all lobes except the right upper. In addition there was extensive embolism of the arteries supplying the brain. The right common carotid artery at its origin contained an embolus, which was several centimeters in length. The right internal carotid artery contained a second embolus, which extended into the right middle cerebral artery. The left anterior cerebral artery contained a third embolus. To complicate

Figure 2. *Photograph of the Pulmonary Valve.*
The right ventricle and pulmonary artery have been opened anteriorly, exposing the normal pulmonary valve and the stenotic subpulmonary tract. The arrows that overlie the sectional surfaces of the anterior wall of the right ventricle point to the limits of the stenotic subpulmonary tract. Two large, warty vegetations are seen attached to the thickened endocardium below the valve.

the cerebral pathology, several of the dural sinuses and many of the cortical veins were filled with darkred thrombi. In the left frontal lobe there was a hemorrhagic infarct of venous origin. The cerebrum showed multiple additional areas of infarction, most of them of arterial embolic origin. All the infarcts were recent but were of slightly varying ages.

In summary, this patient had the tetralogy of Fallot and died of thromboembolic phenomena. We are not sure of the origin of the emboli. The thrombus in the right atrial appendage was relatively fresh, considerably more so than the emboli in the cerebral and pulmonary arteries. The thrombi in the subpulmonary tract were nonbacterial, were composed chiefly of platelets and showed early organization. They also differed in structure from the emboli in the brain and lungs. This bland type of subpulmonary thrombosis is occasionally seen in the tetralogy of Fallot and may increase the degree of stenosis.[5] Possibly, the emboli in the present case came from the leg veins; unfortunately, we did not examine them at autopsy.

An interesting incidental feature of this case was the presence of small crops of fat emboli in the systemic, as well as in the pulmonary, circulation. Patients with a normal circulatory system who have demonstrable fat in the systemic arteries almost always have a fairly large amount of it in the pulmonary circulation as well. In this infant, because of the shunt, fat was more prominent in the cerebral vessels than in the lung. This finding suggests that, along with cerebral abscess and embolism, cerebral fat embolism is a potential hazard to which patients with a right-to-left shunt are more susceptible than normal persons, if subjected to trauma. I do not know that any fatal cases of cerebral fat embolism have been reported in patients with shunts. In this particular case the fat emboli were probably not sufficient in amount to cause any significant symptoms. Where the fat came from I do not know — presumably from bone or soft tissue damaged by convulsions.

DR. FRIEDLICH: How do you know that the cerebral occlusions were emboli rather than thrombi?

DR. SCULLY: The nature of the infarcts, which were mottled with blood, the spotty localization of the occlusions, the microscopical appearance of the occlusions and the coexistence of pulmonary occlusions, which also appeared embolic, make primary thrombosis very unlikely. Regarding cerebral thrombosis, Dr. Jesse E. Edwards,[6] of the Mayo Clinic, believes that it must be a very rare complication of the tetralogy. In his experience, abscess is the most frequent cerebral complication. He thinks that the strong tendency to think of cerebral thrombosis as a complication of the tetralogy has led to unverified clinical diagnoses in cases in which autopsies, if they had been done, would probably have shown abscess formation instead of thrombosis.

DR. BLAND: Were there emboli elsewhere in the body?

DR. SCULLY: There were tiny occlusions in the arterioles of several organs but there were no large emboli except in the brain and lungs.

A PHYSICIAN: Was there any evidence of sepsis at autopsy?

DR. SCULLY: No; there was no evidence of infection anywhere in the tissues; the post-mortem blood cultures were negative.

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CASE 42112

PRESENTATION OF CASE

A thirty-eight-year-old woman entered the hospital because of a sore thumb.

Two months previously she noted the gradual onset of increasing pain and swelling in the right thumb. There was no history of trauma or joint disease. About five months before entry she began having an almost constant deep, aching, nonradiating pain in the chest below the left breast. This pain was unrelated to respiratory movements. She was told that she had "heart trouble." Subsequently, two electrocardiograms were normal. X-ray films of the chest three months before admission showed the heart shadow to be within normal limits in total size, but there was some fullness in the region of the left atrium; the pulmonary vessels were somewhat full; the upper portion of the left hilus in particular seemed full. There was no history of cough or dyspnea.

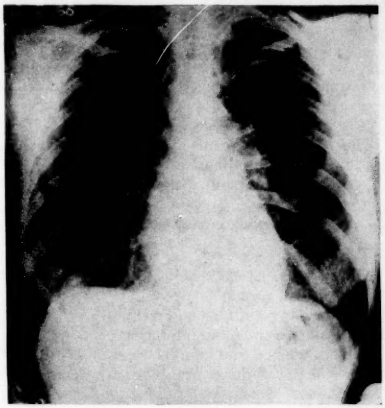

FIGURE 1.

Ten years before admission the patient's first husband had died of pulmonary tuberculosis after an illness lasting four years. There was no past history of rheumatic fever.

Physical examination revealed a painful, tender swelling, with bluish discoloration of the overlying skin and questionable fluctuation, over the dorsum of the first metacarpal region on the right and with displacement but without involvement of the thenar muscles. There was no tenderness about the flexor retinaculum. The motion of the first metacarpophalangeal joint was restricted because of the pain, but there was free movement within a small range. Full extension was possible in the distal interphalangeal joint. There was no lymphadenopathy. Examination

of the chest was negative. No cardiac murmurs were heard.

The temperature was 98.4°F., the pulse 100, and

FIGURE 2.

the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

The urine gave a + test for albumin and a negative test for Bence-Jones protein; the sediment contained 3 red cells and 10 white cells per high-power field. Examination of the blood revealed a hemoglobin of 14.5 gm. per 100 ml. and a white-cell count of 11,200. The total protein was 7.9 gm., the albumin 4.6 gm., the globulin 3.3 gm., the uric acid 1.8 mg., the calcium 8.8 mg., and the phosphorus 2.8 mg. per 100 ml. The alkaline phosphatase was 5.2 units. Widal and brucella agglutinations were negative. X-ray films of the chest showed clear lung fields; the left pulmonary hilus was prominent, and there was a suggestion of a mass in this region with a curved outer border (Fig. 1). An x-ray film of the right hand demonstrated extensive lytic destruction of the first metacarpal bone, with evidence of an associated soft-tissue mass (Fig. 2); all the bones were osteoporotic, especially the proximal and distal phalanges of the thumb. X-ray films of the cervical, thoracic and lumbar spine, skull, ribs and pelvis were normal.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN W. ROPES*: I find it difficult to tie these facts together. The main sites of involvement with disease were obviously the metacarpal bone and the region of the mediastinum. Whether or not the minimal urinary changes and the high globulin were significant is difficult to know. I think that the illness was probably of short duration. The symptoms noted five months before admission, I assume, were the beginning of the present illness. Moreover, I believe that the lesions in the chest were related to the one in the thumb. Before I discuss the diagnosis I should like to see the x-ray films. I should like to ask whether all the other bones were normal. Did the osteoporosis suggest generalized bone involvement?

DR. JOSEPH HANELIN: Only the first metacarpal of the right hand is involved. The other bones are normal. The bony abnormality in the hand consists of an extensive lytic lesion, which has largely destroyed the first metacarpal (Fig. 2). An associated soft-tissue mass can easily be seen. The osteoporosis is probably all secondary to the lytic lesion.

DR. ROPES: It does not involve the joint?

DR. HANELIN: I do not believe there is any joint involvement although the bone is destroyed to the level of the cartilage. The fiims of the chest show prominence at the superior aspect of the left-lung root that is consistent with an enlarged lymph node (Fig. 1). The lungs peripherally are clear. There is some suggestion in the first examination of slight enlargement of the left atrium, but the heart is not enlarged in over-all dimension and there is no obvious engorgement of the pulmonary vessels.

DR. ROPES: I was disturbed when I thought that the process in the thumb extended across the joint. I had the impression that it was not related to the joint directly—that involvement of joint tissue was no more than indirectly present.

The conditions that have to be considered are chronic infection and tumors. I think that generalized bone diseases and metabolic bone diseases can be discarded since the bones elsewhere were normal. It seems to me very unlikely that the lesion in the thumb represented a large area of localized destruction associated with generalized bone disease. It is not likely that this was an acute infectious process. I have never seen these x-ray changes with an acute infection such as an osteomyelitis caused by a pyogenic organism, and there was no systemic reaction suggesting such infection.

Several granulomatous infections have to be considered. Tuberculosis comes to mind first, since the patient's first husband had tuberculosis and there were symptoms of involvement of both the chest and the bones. The symptoms, however, did not suggest tuberculosis. This extremely destructive type of lesion of bone without surrounding reaction would be quite unusual in tuberculosis, as it would in brucellosis. Any granulomatous infection could do this, but no such process seems likely. The three most likely are tuberculosis, sarcoid and brucellosis. They all might explain the high globulin, which I suspect was re-

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lated to the disease. The urinary findings were minimal; without further confirmation of them I should not be convinced that they were part of the disease. If a granulomatous disease was present, I should think that it was coincidental.

There is little likelihood that the entire picture could have resulted from a simple benign tumor. A hemangioma should be considered particularly since there was a bluish discoloration of the overlying skin. However, I think that this probably represented venous distention.

Primary malignant bone tumors also must be considered. I believe Dr. Hanelin will agree that it would be extremely unusual for an osteogenic sarcoma to be present without evidence of osteogenesis and calcification or bone formation. Do you see evidence of osteogenesis?

DR. HANELIN: There is no new bone formation.

DR. ROPES: Therefore, that diagnosis is unlikely.

Among the generalized tumors, myeloma and lymphoma have to be considered seriously. Myeloma could explain the high globulin. Lymphoma could probably explain the minimal urinary findings. There was no Bence-Jones protein, and apparently the other bones, including the skull and vertebras, were normal. Either of these tumors can involve a single bone and can break through the bone. They can cause marked lysis of bone. I think the break through the cortex of the bone would be unusual for these tumors, but either of these conditions may have been present. It is impossible to rule either of them out.

The low uric acid rules out gout, and I think any of the blood dyscrasias is unlikely with such an unusually low uric acid. I am intrigued that this determination was done. I wonder if the physicians thought it was one of the blood dyscrasias. I think at this stage I should mention joints. I believe that this was not a joint disease. This degree of destruction could occur in a joint only with gout, but the overlying involvement did not suggest tophi. I am relatively certain that this was not gout.

One has to consider metastatic tumors too. Before I saw the x-ray films, I suspected that a metastatic tumor would best tie the two sites of disease together. The onset with severe pain deep in the chest suggests the possibility of a malignant lesion in the chest, which may have been missed in the x-ray films taken early in the disease. Such changes are often found in later x-ray examinations. It is surprising that in five months so little obvious progression of a malignant process was present. To think of a lesion that would give these symptoms, be in this localization and metastasize to the hand — a very rare place for metastases — is difficult. In lytic metastatic bone lesions, one has to consider cancer from the breast and from the thyroid gland. I judge that the examination of the breasts was negative and that since the symptoms first started in the region of the breast, they were examined frequently during the five months. Therefore, I shall rule out metastases to the chest and thumb from a cancer of the breast.

Hypernephroma has to be mentioned whenever there is a metastatic lesion in the bone, particularly one that causes lysis. I see nothing in the x-ray picture that looks like a hypernephroma of bone and shall rule that out.

I have discussed a motley array of lesions that can involve the metacarpal bone and chest. I have omitted any mention of the cardiovascular system other than hemangiomas. I believe the chest lesion was not separate from the thumb and was not a manifestation of cardiovascular disease. Among these various, unsatisfactory diagnoses, I think granulomatous infection is unlikely. A malignant process is the most likely. I am torn between lymphoma and the peculiar manifestation of a metastatic lesion to the thumb from the lung — the two most likely but not very satisfying diagnoses; of the two, I favor the latter.

DR. BENJAMIN CASTLEMAN: Dr. Kranes, what do you think this was?

DR. ALFRED KRANES: I am inclined to agree with Dr. Ropes that this was metastatic cancer. There have been a number of reports about metastases from bronchogenic carcinomas to the phalanges. I have seen one.

DR. ROPES: It is very rare, but it can occur.

DR. CASTLEMAN: Dr. Ellis, have you any comment?

DR. DANIEL S. ELLIS: I think that the patient had a metastatic lesion probably from a carcinoma of the thyroid gland or breast.

DR. HELEN S. PITTMAN: The appearance of the lesion in the chest does not, to me, resemble a metastatic tumor of the lung.

CLINICAL DIAGNOSIS

Tuberculosis of metacarpal bone.

DR. MARIAN W. ROPES'S DIAGNOSIS

Carcinoma of lung, with metastasis to metacarpal bone.

ANATOMICAL DIAGNOSIS

Carcinoma of lung, with metastasis to metacarpal bone.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Edwin F. Cave curetted the lesion in the thumb, and the currettings showed a well differentiated adenocarcinoma. After the biopsy, bronchoscopy was performed by Dr. J. Gordon Scannell, who found on the left side what he thought was infiltrating tumor, although he could not see any outcropping of the tumor. He took a biopsy, but we could not find any tumor in it. The mass in the

chest rapidly enlarged, and evidence of effusion in the pericardium soon developed (Fig. 3). An aspiration of the pericardium showed hemorrhagic material, which contained tumor cells. Many more symptoms of tamponade developed, and a window was

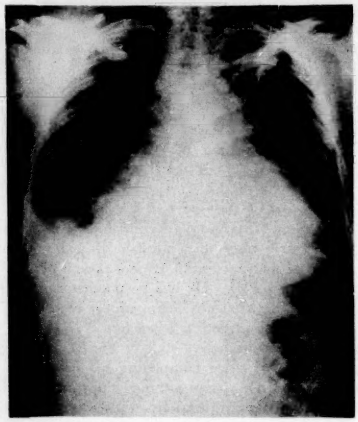

FIGURE 3.

produced in the pericardial cavity for relief. The patient died about six months after the original film of the chest was taken. At autopsy we found that the primary tumor was in the left bronchus. The entire pericardium was filled with tumor. In many places in the lung we could find invasion not only of lymphatics but also of veins. The metastasis to the thumb was certainly blood borne.

DR. HANELIN: At autopsy was the lesion primary in a major bronchus, or was it a peripheral nodule with secondarily enlarged hilar lymph nodes?

DR. CASTLEMAN: There was a peripheral nodule in the upper lobe and a large mass surrounding the bronchus. Although most of this mass was composed of bronchial lymph nodes I believe the primary site was in the bronchus close to the lymph nodes. The tumor was made up of well differentiated acini and probably arose from the glands of the bronchus.

DR. HANELIN: What we visualized initially was only adenopathy. It was difficult to see the primary tumor because the enlarged lymph nodes overshadowed the left interlobar artery. Subsequently, the lesion was obvious, and there was the development of further adenopathy, which was clearly evident. We were able to visualize a nodule behind the left first rib. I think it was our opinion at the time that the lesion was primary peripherally, that the lesion in the vicinity of the hilus was lymphadenopathy, and that there might have been secondary invasion of the bronchus subsequently.

DR. MILFORD D. SCHULZ: How frequent are metastases to the hand?

DR. KRANES: An increasing number of such cases are being reported.

DR. HANELIN: It may well be the most common metastatic lesion to the hand although metastases below the elbows and knees are very rare.

DR. CASTLEMAN: I think that Dr. Merrill C. Sosman believes that metastases to the hand are most frequently from cancer of the lung.

DR. WILLIAM H. BAKER: I followed this patient for six months. She had a strong family history of cancer of the lung. The father and a maternal aunt had died of cancer of the lung. She had smoked 1 or 2 packages of cigarettes daily for many years. The presence of a metastatic lesion in the thumb made us think it was probably from the lung since we had also seen 1 other case.

DR. SCHULZ: Cancer of the cervix metastasizes below the elbows and below the knees.

DR. CASTLEMAN: As a solitary metastasis?

DR. SCHULZ: Not as a solitary metastasis.

Correction. In the paper, "Habilitation of the Cleft Palate," by MacCollum, Richardson and Swanson, which appeared in the February 16 issue of the *Journal*, the sentence beginning on the seventh line under "Time and Method of Repair," on page 299, should read as follows: "It has often been reported in the literature that operation on palates before eighteen months carries considerable risks.[4,5]"

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MAN OF THE YEAR

THE *Journal* takes pride and pleasure in acknowledging as its man of distinction Dr. Chester Morse Jones, who on February 18 received from Williams College the Rogerson Cup and Medal "for outstanding service to the college and for distinction in his field of endeavor." It is not the first time that Williams has recognized this distinguished graduate, for in 1942, the year after he had been loaned by Harvard to Vanderbilt University as acting associate professor of medicine, it conferred on him the honorary degree of Doctor of Science.

Dr. Jones, a graduate of Williams in 1913 and of Harvard Medical School in 1919, has been for a number of years one of the most valued members of the editorial board of the *Journal;* he is in addition an editor of *Gastroenterology*, a contributor on diseases of the digestive tract to a number of textbooks and the author of many scientific papers as well as a book, *Digestive Tract Pain.* He has been outstanding as a clinician and devoted physician, widely recognized as a scientist and respected as a teacher.

A member of the active staff of the Massachusetts General Hospital since completing his internship at that institution, Dr. Jones attained the grade of physician in the Hospital hierarchy in 1928 and has been consulting visiting physician since 1954. He has been clinical professor of medicine at Harvard University since 1940. A consultant in medicine to the Surgeon General's Office from 1944 to 1946, he was a member of the Medical Mission to Austria in 1947 and to Greece and Italy in 1948, under the auspices of the American Unitarian Service Committee in co-operation with the World Health Organization. He has been a member of the American Board of Internal Medicine since 1948, was its secretary and treasurer from 1953 to 1955 and is presently its chairman. He is a member of the American Society for Clinical Investigation, the American College of Physicians, the Association of American Physicians, the American Gastroenterological Society, of which he was president from 1936 to 1937, and the American Clinical and Climatological Society, over which he presided from 1951 to 1952. He has been chosen to deliver this year's annual Shattuck Lecture before the Massachusetts Medical Society.

The selection of a recipient for this highest graduate honor at Williams must have suggested a paraphrasing of Leigh Hunt's well known line:

And lo! Chet Jones's name led all the rest.

PROPHYLACTIC PORTACAVAL SHUNTS FOR ESOPHAGEAL VARICES

ELSEWHERE in this issue of the *Journal* Welch and his colleagues present an excellent plan for the management of upper gastrointestinal hemorrhage from

esophageal varices. The extremely high mortality accompanying this complication of cirrhosis — a matter that, although it has been stressed by many authorities, is still not wholly appreciated — makes this contribution both timely and valuable. A systematic and aggressive approach similar to that which has effectively reduced the mortality from bleeding gastric and duodenal ulcer should be directed toward the problem of the acutely bleeding esophageal varix. The plan described in the paper referred to is sound and seems to merit an extensive trial.

In view of the extremely high mortality of initial hemorrhages from varices, it would obviously be desirable to prevent hemorrhages from occurring. The authors suggest that this be accomplished by prophylactic portacaval shunts. Brick and his associates have reached the same conclusion and have made a similar recommendation. Before this course is adopted generally it seems wise to distinguish between the "clear and present danger" of a bleeding varix and the potential hazard of a varix that has not bled. Moreover, it must be realized that, despite a ten-year period of study, the whole subject of the position of portacaval shunts in the treatment of esophageal varices remains unsettled in the minds of many investigators. And, as Child* pointed out in his Shattuck Lecture last year, although bleeding has been controlled in cirrhosis by portacaval shunts, the lives of the patients cannot be shown to be significantly lengthened. Finally, in a small but appreciable number of patients bypassing of the liver results in serious neurologic and nutritional disturbances. While this is the state of affairs, a general extension of this operation to the patient with varices who has never bled will prove very little unless some type of control study is established.

All surgeons and physicians of experience can cite occasional patients with varices who have bled seriously but under medical management have improved and have had no further hemorrhages for many years. Although this is not the rule, the fact that it occurs at all indicates that there must be some patients with varices who never have a major hemorrhage. How many is not known, and here is the crux of the problem. Until a careful study is done on a large population of cirrhotic patients in whom varices have been demonstrated and the subsequent course of the disease followed for many months and years, no sound answer to the problem of selection can be forthcoming.

It may be assumed that there is a place for prophylactic portacaval shunts in patients with cirrhosis of the liver, but how to select the patient is a problem to which an answer should be sought before every patient with cirrhosis and varices is subjected to this operation. Indeed, even with careful selection and adequate controls, it will take a considerable volume of experience and much time before one can adequately appraise the value of prophylactic shunts. Because of his long experience and interest in this field, no one is better equipped to explore this subject than Dr. Welch. Meanwhile, the position of portacaval shunts both in the treatment of bleeding varices and as a prophylactic measure must remain *sub judice*.

*Child, C. G., III. Shattuck Lecture: portal circulation. *New Eng. J. Med.* 252:837-850, 1955.

SKOAL!

THE journal of the Norwegian Medical Society — *Tidsskrift for Den Norske Laegeforening* — celebrated at the close of 1955 its seventy-fifth year of existence with the publication of a special "Jubileumsnummer," bringing to date the history of the medical progress that the past three quarters of a century has brought to this far northern nation.

The articles comprising the jubilee number, contributed by a group of eminent authors, have been summarized in English by various members of the editorial staff. The first of these papers, by Dr. Peter M. Holst, professor of epidemiology, describes health conditions as they existed around 1880. They were, he admits, medieval in character, for Norway was at that time a poverty-stricken country, economically depressed and losing many of its more resolute citizens through emigration. Conditions in the rural areas and along the coast were indescribably primitive; scarcely 1 farm in 5 could boast a privy, and the annual bath was a luxury indulged in only in the more civilized towns. The death rate was 16 per 1000 inhabitants; 530 physicians served a population of 1,800,000 persons, many of them living in remote areas.

As medicine progressed in such a rugged setting it is natural that the concept of medical service early assumed the character of a social responsibility. This crystallized out, according to Dr. Karl Evang, health director of Norway, into the Health Service Act of 1860, which introduced municipal self-administration as a major policy. Insurance against illness was studied as early as 1885, and compulsory health insurance was adopted in 1911, with state and municipal governments co-operating. Today, writes Dr. Jorgen H. Berner, former secretary general of the Norwegian Medical Society, every employed person is perforce part of the insurance system, and any other citizen may become a voluntary member. Ninety per cent of the population is thus enrolled, under a system of free choice of physician and fee for service, the patient paying the difference when the amount disbursed is less than the full fee.

Articles are included on the contributions to medical progress of Norwegian physicians, the professors at the turn of the century, and a description (in English) by Dr. Gunnar Gundersen, of La Crosse, Wisconsin, of the influence of Norwegian medicine in the United States. The Norwegian emigration to this country began in 1825 as a search for religious freedom, so these pioneers were accompanied by their pastors rather than by their physicians. The first of

the doctors to arrive was Hans Christian Brandt, in 1840; among the later arrivals were Dr. Adolf Gundersen, in 1891, who founded not only the Gundersen Clinic in La Crosse but the Gundersen medical dynasty, and Boston's own Marius N. Smith-Petersen, who reached these shores soon after the turn of the century. Hektoen, Adson and Wangensteen are among the country's notable physicians of Norwegian descent.

The *Tidsskrift* was first privately published in January, 1881, by three physicians of Christiania — M. Skjelderup, F. Stabell and Caesar Boeck who, eighteen years later, gave the first description of "Multiple Benign Sarcoid of the Skin." From the beginning the periodical was outspoken and courageous, policies that have marked its course throughout its ownership by the Norwegian Medical Society, to which it was offered as a gift when that organization was founded in 1886. The present incumbent of the editorial chair, Dr. Jens Bjørneboe, has skillfully and devotedly guided the journal's destinies since 1945 and, it may be hoped, will see it to its century mark.

NUPTIAL INDEX

THE astute statisticians of the Metropolitan Life Insurance Company, according to a recent release from the Information Service of that organization, foresee no appreciable change in the marriage rate during 1956. The prediction is based not only on a study of the annual matrimonial index over a number of years, but on an equally careful investigation into the marital potentials of leap year, if any.

The subject of marriage and its implications has for some time reverberated through the editorial pages of the *Journal*. In an editorial, "Wedlock and the Birthrate," published in the issue of September 9, 1954, certain statistics on these domestic relations, emanating from the Department of Health, Education and Welfare, are the subject of comment. From the figures released at that time it appeared that births for the first four months of 1954 had increased by 30,000 over those for the corresponding period in 1953, whereas 25,000 fewer marriages had been celebrated. The disparity was due to other and more complicated factors than might appear at first glance.

A more recent editorial, emanating, like the present one, from the statistical workshop of the Metropolitan Life Insurance Company, indicates that the typical American housewife, of which there are currently some 40,000,000, is relatively young, lives in her own home in an urban area, and is actively engaged in raising a family. Fifty per cent of her number have become married since 1940, 94 per cent live with their husbands, and 22 per cent are also otherwise employed.

According to the more recent release forming the basis of this discussion it is estimated that 1,532,000 marriages took place in the United States during 1955, representing a 3 per cent increase over the 1954 total of 1,488,000 such unions, although still below the 1,545,000 marriages of 1953. No great change is expected, in fact, until after the early 1960's, when the war babies of the roaring 40's reach marriageable age.

The slight rise in the marriage market of yesteryear was most marked in the Pacific and Mountain regions. Of the five largest cities New York alone recorded a decrease, with little or no change in Chicago and Philadelphia and an increase of approximately 6 per cent in Los Angeles and Detroit.

There is now living in the neighborhood of Glasgow, a lady in her 107th year; and very recently another female is reported to have died at the age of 101; whilst a carpenter, named John Walney, died in Glasgow during 1757, actually 124 years old. This man is stated to have married eleven wives, all of whom he buried; and of his seventeen children five survived him, whose ages amounted to 326 years collectively.

Boston M. & S. J., *March 20, 1856*

MASSACHUSETTS MEDICAL SOCIETY

APPLICANTS FOR FELLOWSHIP

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University of Vermont College of Medicine, 1950.

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Harvard Medical School, 1950.
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Tufts College Medical School, 1952.
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Tufts College Medical School, 1947.
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Harvard Medical School, 1950.
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Tufts College Medical School, 1954.
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Harvard Medical School, 1948.
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Tufts College Medical School, 1951.
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Boston University School of Medicine, 1951.
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State University of New York College of Medicine, New York City, 1950.
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Midwest Medical College, 1934.
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Harvard Medical School, 1947.
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Harvard Medical School, 1950.
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George Washington University School of Medicine, 1936.
STERNFELD, LEON, Health Department, Room 309, City Hall, Cambridge.
University of Chicago, The School of Medicine, 1936.
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University of Rochester School of Medicine and Dentistry, 1949.

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Cornell University Medical College, 1950.

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Harvard Medical School, 1946.

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Boston University School of Medicine, 1952.

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Harvard Medical School, 1950.

PRYLES, CHARLES VICTOR, Boston City Hospital, Boston.
University of Georgia School of Medicine, 1947.

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Harvard Medical School, 1948.

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Tufts College Medical School, 1947.
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The Medical College of the State of South Carolina, 1951.
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Harvard Medical School, 1951.
WALSH, JOHN WALTER, Veterans Administration Clinic, 17 Court Street, Boston.
New York State University (Long Island College of Medicine), 1942.
WILLER, LEE HERBERT, 479 Beacon Street, Boston.
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Harvard Medical School, 1949.

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University of Virginia, Department of Medicine, 1951.
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University of Vermont College of Medicine, 1944.
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Tufts College Medical School, 1951.
ROSEN, THEODORE, 23 Westminster Street, Fitchburg.
Middlesex College of Medicine and Surgery, 1937.
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NORWOOD, ROBERT FLEMING, Florida, at present.
University of Michigan Medical School, 1952.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1956

RÉSUMÉ

DISEASE	JANUARY 1956	JANUARY 1955	SEVEN-YEAR MEDIAN
Chancroid	0	4	4
Chicken pox	2257	2221	2221
Diphtheria	0	1	4
Dog bite	595	599	611
Dysentery, bacillary	3	3	3
Encephalitis, infectious	1	4	3
German measles	152	216	142
Gonorrhea	164	185	196
Granuloma inguinale	0	0	0
Hepatitis, infectious	32	161	10
Lymphogranuloma venereum	2	4	1
Malaria	0	0	0
Measles	429	12531	840
Meningitis, meningococcal	11	14	7
Meningitis, Pfeiffer bacillus	4	10	6
Meningitis, pneumococcal	10	0	3
Meningitis, staphylococcal	1	1	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	6	6
Mumps	291	1932	1666
Poliomyelitis	8	1	2
Salmonellosis	49	14	6
Scarlet fever	452	610	549
Syphilis	180	152	152
Trichinosis	1	1	1
Tuberculosis, pulmonary	172	184	185
Tuberculosis, other forms	7	13	13
Typhoid fever	1	2	0
Undulant fever	1	0	1
Whooping cough	66	308	308

COMMENT

Diseases below the seven-year median were diphtheria, measles, mumps, scarlet fever and whooping cough.

For the first time in the history of the State no cases of diphtheria were reported during the month of January.

The 291 cases of mumps reported during January makes this the lowest figure for the disease for this month since 1919.

During January whooping cough was at its lowest level for this month in the history of the State.

Diseases above the seven-year median were infectious hepatitis, poliomyelitis, salmonellosis, chicken pox and German measles.

Although infectious hepatitis was above the seven-year median during January, this represented the twelfth consecutive month in which a decrease from the corresponding month of the previous year was registered.

During January salmonellosis was at the highest level for this month in the history of the State.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Actinomycosis: Waltham, 1.

Dysentery, bacillary: Peabody, 1; Springfield, 1; Worcester, 1; total, 3.

Encephalitis, infectious: Worcester, 1.

Hepatitis, infectious: Boston, 4; Chelsea Naval Hospital, 2; Dartmouth, 1; East Longmeadow, 1; Fall River, 3; Falmouth, 1; Framingham, 1; Holyoke, 4; Lawrence, 1; Lowell, 2; Medford, 1; Newton, 2; Rockport, 1; Somerville, 3; Taunton, 2; Westfield, 1; Worcester, 2; total, 32.

Meningitis, meningococcal: Cambridge, 1; Clinton, 1; Dighton, 1; Fall River, 1; Lynn, 2; Melrose, 1; Salem, 1; Walpole, 1; Waltham, 1; Wellesley, 1; total, 11.

Meningitis, Pfeiffer bacillus: Swampscott, 1; Wellesley, 1; Weymouth, 1; Worcester, 1; total, 4.

Meningitis, pneumococcal: Boston, 2; Brockton, 1; Cambridge, 1; Gardner, 1; Lowell, 1; Peabody, 1; Springfield, 2; Taunton, 1; total, 10.

Meningitis, staphylococcal: Taunton, 1.

Meningitis, undetermined: Barnstable, 1; Belchertown, 1; Milford, 1; Watertown, 1; total, 4.

Poliomyelitis: Everett, 1; Groton, 1; Lynn, 1; Marblehead, 1; Medford, 1; Millis, 1; South Hadley, 1; Weymouth, 1; total, 8.

Psittacosis: Boston, 1; Cambridge, 1; total, 2.

Salmonellosis: Belchertown, 1; Beverly, 1; Boston, 2; Cambridge, 1; Chicopee, 1; Danvers, 1; Fitchburg, 2; Framingham, 1; Hamilton, 1; Lowell, 2; Lynn, 6; Lynnfield, 2; Milford, 1; Needham, 1; Newton, 4; North Attleboro, 3; Quincy, 2; Randolph, 1; Saugus, 3; Somerville, 4; Springfield, 2; Wakefield, 1; Watertown, 3; Wellesley, 3; total, 49.

Tetanus: Lowell, 1.

Trichinosis: Boston, 1.

Typhoid fever: Worcester, 1.

Undulant fever: Holden, 1.

CORRESPONDENCE

REGARDING PHYSICIAN AND PHARMACIST

To the Editor: Regarding the editorial, "Physician and Pharmacist," in the February 9 issue of the *Journal*, I wonder why representatives of the Massachusetts Medical Society did not have a paragraph inserted in the bill to protect physicians, similar to that of the veterinarians, which gave them the right to dispense or sell drugs as required in their practice.

It should not be too hard to convince legislators that there are times, especially in rural districts, when it would be a hardship for a patient to get up from a sick bed and travel miles on a stormy night to get a prescription filled after the drugstore was closed.

MILMAN PEASE, M.D.

Brookfield, Massachusetts

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held January 19, 1956, it was voted to suspend the registration of Dr. Hederea Reina, Hathorne, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEW

Breast Cancer: Its diagnosis and treatment. By Edward F. Lewison, M.D. 4°, cloth, 478 pp., with 181 illustrations and 92 tables. Baltimore: The Williams and Wilkins Company, 1955. $15.00.

A timely and well presented textbook on this important problem. The author has had the collaboration of many authorities in this field. The whole presentation is orderly and well written. The illustrations are adequate and excellent.

The chapter on the history of cancer is extremely interesting. Due to the accessibility of the breast, it is easy to understand why early concepts of malignant disease would be concentrated on this organ.

This volume will be of inestimable value as a reference book for students and practitioners.

ARTHUR W. ALLEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Röntgenschichtverfahren: Grundlagen der technischen Entwicklung und der klinischen Anwendung für die Praxis. By Prof. Dr. R. Griesbach, Augsburg; and Dr. F. Kemper, Frankfurt/Main. 4°, cloth, 143 pp., with 92 illustrations. Stuttgart: Georg Thieme, 1955. DM 39.- $9.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Gynecology: Surgical techniques. Compiled and edited by Robert J. Lowrie, M.A., M.D., D-OG., associate clinical professor of obstetrics and gynecology, College of Medicine, New York University, attending gynecologist and obstetrician, St. Vincent's Hospital, senior attending obstetrician, City Hospital, Welfare Island, and attending gynecologist, Willard Parker Hospital. With a foreword by J. P. Greenhill, M.D. 4°, cloth, 523 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1955. $17.75.

The Hemorrhagic Disorders: A clinical and therapeutic approach. By Mario Stefanini, M.D., associate professor of medicine, Tufts University School of Medicine, director of Research Laboratories and hematologist, Saint Elizabeth's Hospital, Boston, and established investigator, American Heart Association; and William Dameshek, M.D., professor of medicine, Tufts University School of Medicine, and senior physician and director, Blood Research Laboratory, New England Center Hospital, Boston. 4°, cloth, 368 pp., with 147 illustrations and 37 tables. New York: Grune and Stratton, Incorporated, 1955. $11.75.

Magic and Schizophrenia. By Géza Róheim. Posthumous edition by Warner Muensterberger, Ph.D., with the assistance of S. H. Posinsky, Ph.D. With a foreword by Sandor Lorand, M.D. 8°, cloth, 230 pp. New York: International Universities Press, Incorporated, 1955. $4.50.

Progress in Neurology and Psychiatry: An annual review. Vol. 10. Edited by Ernest A. Spiegel, M.D., professor of experimental neurology and head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. 8°, cloth, 645 pp. New York: Grune and Stratton, Incorporated, 1955. $10.00.

A Handbook of Hospital Psychiatry: A practical guide to therapy. By Louis Linn, M.D., assistant attending psychiatrist, Mount Sinai Hospital, New York City. 8°, cloth, 560 pp. New York: International Universities Press, Incorporated, 1955. $10.00.

A Stereoscopic Atlas of Human Anatomy: Section III: The upper extremity: Reels 85 - 112. By David L. Bassett, M.D., associate professor of anatomy, Stanford University, California. 8°, paper, profusely illustrated with color photographs by William B. Gruber. Portland, Oregon: Sawyer's Incorporated, 1955.

Medical Research: A midcentury survey. Vol. 1. *American Medical Research: In principle and practice.* 8°, cloth, 765 pp. Vol. 2. *Unsolved Clinical Problems: In biological perspective.* 8°, cloth, 740 pp. $15.00. - 2 volumes. Boston: Little, Brown and Company, 1955. (Published for the American Foundation.)

Thromboembolic Disease. By Geza de Takats, M.D., M.S., Division of Vascular Surgery, Department of Surgery, University of Illinois College of Medicine, and Research and Educational Hospital, St. Luke's Hospital, Chicago. 8°, paper, 55 pp. Springfield, Illinois: Charles C Thomas, 1955. $2.25. (Publication No. 286, *American Lecture Series.*)

Practical Neurology. By Leo M. Davidoff, M.D., professor of surgery and chairman, Department of Surgery, Albert Einstein College of Medicine, director of surgery, Bronx Municipal Hospital Center, and chief of neurosurgery, Mount Sinai Hospital, New York City; and Emanuel H. Feiring, M.D., associate professor of surgery (neurosurgery), Albert Einstein College of Medicine, visiting surgeon (neurosurgery), Bronx Municipal Hospital Center, and associate neurosurgeon, Mount Sinai Hospital, New York City. 8°, cloth, 442 pp. New York: Landsberger Medical Books, Incorporated, 1955. $7.00. (Distributed solely by the Blakiston Division of the McGraw-Hill Book Company.)

Functional Otology: The practice of audiology. By Morris F. Heller, M.D., assistant attending otolaryngologist for audiology and chief of the Audiology Clinic, Mount Sinai Hospital, New York City. With Bernard M. Anderman, M.A.; and Ellis E. Singer, M.A. 8°, cloth, 225 pp., with 31 illustrations and 3 tables. New York: Springer Publishing Company, Incorporated, 1955. $5.50.

Amputees and Prostheses: Report of a conference on prosthetics, Copenhagen, 23-28 August, 1954. 8°, paper, 52 pp., with 7 illustrations and 9 tables. Geneva: World Health Organization, 1955. (No. 100, *World Health Organization Technical Report Series.*) $0.60. (Distributed in the United States by Columbia University Press, International Documents Service, New York City.)

Glaucoma: A symposium organized by the Council for International Organizations of Medical Sciences: Established under the joint auspices of UNESCO and WHO. Edited by Sir Stewart Duke-Elder, England. 8°, cloth, 350 pp., with illustrations, tables, charts and a frontispiece. Springfield, Illinois: Charles C Thomas, 1955. $7.50.

Hand Surgery in World War II. Edited by Sterling Bunnell, M.D. 4°, cloth, 447 pp., with 224 illustrations and 4 tables. Washington, D.C.: Office of the Surgeon General, Department of the Army, 1955. (Medical Department, United States Army.) $3.75.

Preventive Medicine in World War II. Vol. 2. *Environmental Hygiene.* Colonel John Boyd Coates, Jr., M.C., editor-in-chief; and Ebbe Curtis Hoff, Ph.D., M.D., editor for preventive medicine. 4°, cloth, 404 pp., with 25 illustrations and 7 charts. Washington, D.C.: Office of the Surgeon General, Department of the Army, 1955. (Medical Department, United States Army.) $3.50.

The Cornea. By Charles I. Thomas, M.D., associate clinical professor of ophthalmology, Department of Surgery, Western Reserve University School of Medicine, and associate ophthalmologist, Department of Surgery, University Hospitals of Cleveland. 8°, 1318 pp., with 400 illustrations and 13 tables. Springfield, Illinois: Charles C Thomas, 1955. $30.00.

Junior Intern. By Alan E. Nourse. 8°, cloth, 210 pp. New York: Harper and Brothers, 1955. $2.50.

Obstetrical Practice. By Alfred C. Beck, M.D., consultant in obstetrics and gynecology, Long Island College Hospital, St. Peter's Hospital and Norwegian Hospital, Brooklyn, New York, United States Naval Hospital, St. Albans, New York, Vassar Brothers Hospital and St. Francis Hospital, Poughkeepsie, New York; and Alexander H. Rosenthal, M.D., clinical associate professor of obstetrics and gynecology, State University of New York College of Medicine at New York City, chief obstetrician and gynecologist, Long Island Jewish Hospital, New Hyde Park, New York, and attending obstetrician and gynecologist, Kings County Hospital, New York. Sixth edition. 4°, cloth, 1066 pp., with 947 illustrations, 8 tables, 2 charts and 23 plates. Baltimore: The Williams and Wilkins Company, 1955. $12.00.

The Surgical Technic of Abdominal Operations. By Julius L. Spivack, M.D., LL.D., associate professor of surgery, University of Illinois College of Medicine, and senior attending surgeon, Columbus Memorial and Mother Cabrini hospitals, Chicago. Fifth edition. 4°, cloth, 931 pp., with 495 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $17.50.

NONCLINICAL NOTES

AMERICAN SOCIETY FOR SURGERY OF THE HAND

Dr. J. Edward Flynn, director of the hand clinic of the Boston City Hospital, was chosen president-elect of the American Society for Surgery of the Hand at the eleventh annual meeting in Chicago on January 27.

NOTICES

BOSTON EVENING CLINIC PSYCHIATRIC CENTER

The Boston Evening Clinic announces the opening of an Evening Psychiatric Center for evaluation and individual and group therapy. The Psychiatric Center will be open on Mondays and Thursdays, from 6 to 9 p.m., by appointment only. All new patients will be admitted on Thursdays. Staff members of the Psychiatric Center are as follows: psychiatrist-in-chief, Dr. Stanley Kanter; consultant, Dr. Arthur Berk; assistant psychiatrists, Drs. William Van Duyne and Patricia Neeley; and social-service consultant, Golda Edinburg. Only patients referred from doctors, clinics, hospitals and social-service departments will be accepted.

BENJAMIN WATERHOUSE MEDICAL HISTORY SOCIETY

A dinner meeting of the Benjamin Waterhouse Medical History Society of Boston University School of Medicine will be held in the Musket Room of the Howard Johnson Restaurant at 870 Massachusetts Avenue and Southampton Street, Roxbury, on Monday, April 2, at 6 p.m. The program is scheduled for 7:30, when Dr. William Malamud will speak on the subject "History of Psychiatry."

NEW ENGLAND CONFERENCE ON HUMAN NUTRITION

The New England Conference on Human Nutrition, sponsored by the Florida Citrus Commission, will be held at the Sheraton Plaza, Boston, on Thursday and Friday, March 22 and 23. Conference subjects are entitled "Nutritional Requirements Among the Population," "The Extent and Impact of the Nutrition Problem in the U.S." and "Implications for Action."

MASSACHUSETTS HEART ASSOCIATION

The Kidney Section of the Massachusetts Heart Association will hold a meeting at the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, March 26, 1956, at 8 p.m.

Dr. Robert Platt will talk on "Some Renal Investigations of Current Interest." Physicians and medical students are invited.

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Massachusetts Society of Anesthesiologists will be held at the Beverly Hospital, Beverly, Massachusetts, on Friday, April 6, at 8 p.m.

Dr. Jacob Fine will be chairman of the panel discussion on "Anesthesia for Emergency Surgery."

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The yearly supper meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club of Boston, on Wednesday, March 28. After the supper Dr.

Dwight E. Harken will give a talk on "Recent Advances in Heart Surgery." Dr. Harken will also show colored moving pictures and slides of his recent work in heart surgery.

All interested physicians are invited to attend.

INTERNATIONAL MEDICAL-SURGICAL MEETINGS

The International Medical-Surgical Meetings will be held, together with the International Exposition, in the Palace of Expositions at the Valentino, Turin, Italy, June 1-9, 1957. As part of the Meetings the Third International Medical and Scientific Film Festival will be held, and the Third International Exposition of Sanitary Arts will present a vast organic picture of advances made in recent years in the various branches of medicine, surgery and hygiene, under their numerous scientific, technical and practical aspects.

SOCIETY MEETINGS AND CONFERENCES

MARCH 15-17. American Orthopsychiatric Association. Page 86, issue of January 12.

MARCH 19 and 21. Josiah Macy, Jr., Foundation Lectures. Page 400, issue of February 23.

MARCH 19-22. American Academy of General Practice. Page 1092, issue of December 15.

MARCH 19-28 and JUNE 4-13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

MARCH 19, APRIL 2 and 16. Hartford Medical Society. Page 242, issue of February 2.

MARCH 20. South End Medical Club. Page 443, issue of March 1.

MARCH 20-28. Consultation Clinics for Crippled Children in Massachusetts. Page 440, issue of March 1.

MARCH 20, 27 and APRIL 3. Boston City Hospital House Officers' Association. Page 297, issue of February 9.

MARCH 21. New England Pediatric Society. Page 347, issue of February 16.

MARCH 21, 22 and 23. Medical and Dental Symposium. Page 347, issue of February 16.

MARCH 21 and APRIL 25. Massachusetts Heart Association. Page 490, issue of March 8.

MARCH 21 and APRIL 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

MARCH 22 and 23. New England Conference on Human Nutrition. Page 539.

MARCH 24 and 25. American Psychosomatic Society. Page 491, issue of March 8.

MARCH 26. Massachusetts Heart Association. Page 539.

MARCH 28. Massachusetts Society of Examining Physicians. Page 539.

MARCH 28 and APRIL 18. Greater Boston Medical Society. Page 208, issue of August 4.

APRIL 2. Fried Lecture Series. Page 535, issue of September 22.

APRIL 2. Benjamin Waterhouse Medical History Society. Page 539.

APRIL 3. Third Microcirculatory Conference. Page 399, issue of February 23.

APRIL 4. New England Surgical Society. Page 347, issue of February 16.

APRIL 5. Second Annual Symposium on Cardiovascular Disease. Page 490, issue of March 8.

APRIL 6. Massachusetts Society of Anesthesiologists. Page 539.

APRIL 7. American Congress of Physical Medicine and Rehabilitation. Page 491, issue of March 8.

APRIL 8. American College of Gastroenterology. Page 491, issue of March 8.

APRIL 12. Nu Sigma Nu Fraternity. Page 491, issue of March 8.

APRIL 15-20. American College of Allergists. Page 399, issue of February 23.

APRIL 16-21. American Academy of Pediatrics. Page 399, issue of February 23.

APRIL 23-26. International Academy of Proctology. Page 399, issue of February 23.

MAY 1-5. Sixth National Congress on Pediatrics. Page 491, issue of March 8.

MAY 2. Postgraduate Medical Institute. Page 487, issue of September 15.

MAY 3-5. American Goiter Association. Page 348, issue of August 25.

MAY 14-18. American Nurses' Association. Page 491, issue of March 8.

MAY 28-JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.

JUNE 1-9. International Medical-Surgical Meetings. Notice above.

JUNE 21-23. Society of Nuclear Medicine. Page 1092, issue of December 15.

JUNE 21-24. American Academy of Dental Medicine. Page 944, issue of December 1.

AUGUST 19-23. American College of Chest Physicians. Page 840, issue of November 10.

SEPTEMBER 3-5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.

SEPTEMBER 10-14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 22

THURSDAY, MARCH 22

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.

*8:45-9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00-10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00-10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

*10:00-11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m. Guest Speaker of the Bingham Associates. Dr. Orvar Swenson. Cape Cod Hospital, Hyannis, Massachusetts.

*11:00 a.m.-12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.

*11:00 a.m.-12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.-12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*11:15 a.m. Thoracic Conference. Acute and Chronic Infections of the Lung. Dr. Paul Fremont-Smith. Main Amphitheater, Peter Bent Brigham Hospital.

*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.

*12:00 m.-1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.

*12:15-1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

*1:00-4:00 p.m. Medical and Dental Symposium. General Session. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

FRIDAY, MARCH 23

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30-11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.

*12:00 m. Urological Conference. Dr. C. J. E. Kickham. Auditorium, Carney Hospital, Dorchester.

*1:00-3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*1:30-4:00 p.m. Medical and Dental Symposium. General Session. Joslin Auditorium, New England Deaconess Hospital.

*2:00-3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.

*4:00-6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Pratt Lecture Hall, Pratt Diagnostic Hospital.

*4:00-10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, MARCH 24

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00-9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*8:30-10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, and J. M. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.

9:00 a.m. American Psychosomatic Society. Sheraton Plaza Hotel, Boston.

*9:30-11:00 a.m. Surgical House Officers' Conference. Second Floor Conference Room, Carney Hospital, Dorchester.

*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, MARCH 26

*8:00-8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30-9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30-11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.-12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.

(Concluded on page xlii)